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THE MONTH

IMMUNIZATION now plays such an important part in medical practice that we have decided to devote an entire symposium to its consideration. The title of the symposium—'Immunization in General Practice'—describes its scope. This is no academic survey of the subject, but a review of the practical applications: the indications and contraindications, the timing, and the dosage. The time was ripe for such a review. During recent years, as the number of immunization procedures has steadily increased, conflicting views have developed among the experts as to how and when these various procedures should be combined. As a result it has become difficult for the general practitioner to decide what is best for his patients. Earlier this year, at a symposium on 'Immunization in Childhood', sponsored by The Wellcome Foundation, many of these difficulties were thrashed out and solved. The majority of the contributors to our symposium took part in the Wellcome symposium and have therefore been able to base their recommendations upon the findings of this expert group. The result is a review of the subject which is both authoritative and completely up to date.

The Symposium

HAS the time not come for a lull in the spate of reports on coronary artery disease? The problem is quite serious enough in all conscience, but it has become so bedevilled by controversy and irrelevant minutiæ that it is becoming impossible for the practitioner to make head or tail of the torrent of reports that pour forth on the subject from statisticians, epidemiologists, biochemists and nutritionists. The time has come when every department working on this problem should adopt as its motto the Swiss inscription: *Schweigen ist golden*. If the members of such departments would only take a Sabbatical year and spend it browsing over the available data we might very well achieve considerable progress.

Coronary Artery Disease

Meanwhile those who wish to obtain as balanced a view as is possible of the present position will find it in two excellent articles in the *Monthly Bulletin of the Ministry of Health*. In the first (1959, **18**, 94), J. M. G. Wilson and M. A. Heasman provide what they describe as 'an epidemiological review' of the subject. One of the fundamental facts to which they draw attention is the lack of evidence as to the actual increase there has been in coronary artery disease. For instance, they point out that the Registrar General has

presented evidence to show there is at present a tendency on the part of clinicians to overdiagnose coronary disease. Their own conclusion is that 'the actual increase in deaths from coronary heart disease is considerably smaller than that shown in official statistics'. An interesting point to which they draw attention is the higher incidence of deaths from this cause in the north and west of the country. Is this due to different habits of certification, varying socio-economic conditions, or a difference in diet and weather? In the second article (*ibid.*, p. 118) W. T. C. Berry discusses the relationship of exercise and dietary fat to the disease. Even here, where the correlation is closer than in the case of many other alleged causative factors, the evidence is by no means convincing. It may well be that, as in so many other branches of medicine, the modern research worker is becoming so bemused by the magic of numbers that he is overlooking the fact that Man is an individual and not merely a replica of every other member of the human race.

Road Accident Figures

In his Motoring Notes this month our Motoring Correspondent draws attention to a disturbing feature of the premises upon which the official road accident statistics are based. According to 'Road Accident Statistics', published by the Royal Society for the Prevention of Accidents, which is the official publication on the subject, the definition of a 'person seriously injured' is: 'A non-fatal casualty who sustained fracture, concussion, internal injury, crushing, severe cuts or lacerations, severe general shock necessitating medical treatment, and any other injury resulting in detention in hospital'. The definition of a 'person slightly injured' is: 'A non-fatal casualty who received injury of a minor character such as sprains or bruises. (Excludes a person complaining of shock but with no other injury, unless exhibiting some clear symptom of shock and receiving or appearing to need medical treatment)'.

If these definitions mean anything—and presumably they do—they mean that if, in 1958, for instance, a person was involved in a road accident (officially defined as 'an accident reported to the Police involving one or more vehicles on the public highway and resulting in at least one human casualty') and bruised his leg he was solemnly placed among the 224,631 'slightly injured' casualties. If, on the other hand, he fractured a phalanx he would appear as one of the 69,166 'seriously injured'. In other words, as our Motoring Correspondent points out, 224,631 of the 299,767 road casualties last year 'suffered injuries no more serious than the sprains or bruises . . . which many people sustain without ever consulting their practitioners'. Further, it may well be asked, how many of the 69,166 'seriously injured' had anything more serious than a Colles' fracture or a broken finger? To magnify the seriousness of the position with regard to road-accident casualties in this way shows a disturbing lack of responsibility on the part of those who compile these figures. To quote our Motoring Correspondent again, 'The figures for deaths and those seriously injured are

bad enough, and it would be far better if the whole emphasis were placed on them in road safety propaganda'. The time has come for a radical revision of these archaic and unjustified definitions.

Fresh-Frozen Milk

THE announcement that a process has been evolved whereby fresh British dairy milk will be available in any part of the world opens up tremendous possibilities, not only for the dairy industry in this country, but also for the provision of increased supplies of fresh milk in the underdeveloped countries of the world. The process, which has been evolved at the National Institute for Research in Dairying, consists of treating pasteurized milk with ultrasonic vibrations of about a million cycles a second for five minutes, and then pouring it into containers for quick freezing. Unlike the currently available frozen homogenized milk, when it is thawed out it returns to a completely natural state without any alteration in condition or taste. The process keeps the milk 'fresh-frozen' for eighteen months provided the temperature of the milk itself is kept below 8°F. (13.3°C.).

This last fact means that the milk can be transported anywhere, particularly to tropical countries where fresh milk supplies are not normally available. Preliminary investigations in the Middle East have shown that there is likely to be a considerable demand for it, and the view has been expressed that with the expansion of cold storage in the Middle East fresh-frozen British milk should in time replace the various canned substitutes for fresh milk now in use. This is the more likely to occur as the retail price for fresh-frozen milk is only a little more than for canned sterilized milk. Travellers by sea are also likely to benefit. Hitherto they have had to be satisfied with tinned milk after the first few days at sea. One shipping line already uses it—storing enough for the return trip to Australia, and thereby guaranteeing their passengers a regular supply of fresh milk. F.A.O. is also interested in the possibility of distributing surplus milk in fresh-frozen form to children in refugee camps and in underdeveloped countries.

Strikes and Cascara

BECAUSE of shortage of supplies there has been a sharp advance in the price of cascara on the London drug market. At the moment the price is running around 275*s.* a hundredweight (50 kg.), compared with 210*s.* in January. According to the *Pharmaceutical Journal*, this is because American lumberjacks have not gone on strike this year! The story behind this curious state of affairs is an interesting one.

The only source of cascara bark is the forests on the Pacific side of North America. Normally lumberjacks bring in supplies to various depots from stocks they have accumulated while on strike for higher wages. Hitherto regular supplies have been assured because, in the words of the *Pharmaceutical Journal*, 'as in other parts of the world, this [a strike] occurs

annually'. After the last strike, however, a three-years' agreement was reached, so this year they have not had the opportunity to collect the bark. Since there are no loggers' stocks available, supplies will be largely dependent upon schoolboys and others who make a few extra dollars by cutting bark near their homes. As this, of course, will be nothing like enough to meet the normal requirements, the price is likely to rise still further on both sides of the Atlantic. Fortunately, by no stretch of imagination can cascara be described as an essential drug, but the apparently steady supply of bark in the past is an interesting commentary on the extent to which the strike has become a routine means of enforcing a rise in wages.

The Irish Resurrectionists

EDINBURGH and London have always been looked upon as the two most notorious centres for the resurrectionists, or body-snatchers, in the days when bodies for the dissecting-room were hard to come by. Dublin, however, would appear to have equal claims to fame (or notoriety) in this respect, according to a fascinating article by John F. Fleetwood on 'The Irish Resurrectionists' in *The Irish Journal of Medical Science* (July 1959, p. 309). He tells, for instance, how the Dublin medical students would dress in ragged clothes and carry a coffin filled with stones to the graveyard. Masquerading as mourners, they would fraternize with others who were guarding the remains of their own relatives. A bottle of whiskey well fortified with opium would then be produced, the students taking care not to participate. Soon the other mourners would be lying helpless round the stone-filled coffin while the students decamped with 'bona fide remains'.

There is what some would describe as a real Irish touch about the story of the malefactor condemned to death who sold his body to the surgeon. With the proceeds he bought a large quantity of liquor and spent his last night drinking and playing cards with his friends. 'A final macabre touch' was provided by the fact that the 'card table' was the condemned man's coffin. So lucrative became this morbid business that, according to Dr. Fleetwood, 'in the 1820's one of our major, if illicit, exports was of dead bodies'. The prime organizer of this gruesome line in exports was a half-pay army surgeon, named Rae (or Ray). He obtained his merchandise by bribing the regular suppliers of the Dublin medical schools to divert the bodies to him. One of the boats regularly plying between Dublin and Glasgow was used and apparently little effort was made to conduct the business secretly. In the end he was caught and lodged in Newgate. With true Hibernian impartiality, Dr. Fleetwood refuses to damn the resurrectionists out of court. 'Ruffians, scoundrels, sordid opportunists', he says, 'they may have been, but they played their part in keeping the anatomy schools alive, and without the basic knowledge of anatomy there can be no medicine and no surgery, so that without them there would have been no Corrigan, no Graves, no Colles, no Stokes, to bring the fame of Irish medicine to every corner of the then known globe'.

SMALLPOX IMMUNIZATION

By C. METCALFE BROWN, M.D., D.P.H.

Medical Officer of Health, City of Manchester and Manchester Port Health Authority

Of Wallingford in 1518 it is recorded 'They do die in these parts . . . of the small pokkes and mezils', and Wallingford was no better and no worse than the rest of the country. They no longer die of smallpox in Berkshire—there was one death from this disease in England and Wales in 1958 (in Cheshire) but they do die in large numbers elsewhere: for example, India and Pakistan together have some 50,000 deaths annually. Smallpox is rife also in many other parts of the world.

The protective value of vaccination has been proved conclusively but protection is not absolute, nor for that matter is the immunity produced by an attack of smallpox although second attacks are very rare indeed.

The Chief Medical Officer in his report of the Ministry of Health (1958) reminds us that smallpox is no longer endemic in Europe; that the chances of exposure to the disease in this country are remote; that vaccination is a prerequisite for travel or entry into any country and is obligatory for service with the Armed Forces. It follows that an increasing number of people will need to be vaccinated at some time or other. The risks of primary vaccination are smaller in infancy than at other ages. It is prudent therefore to vaccinate in infancy to protect against smallpox and to diminish the risks of primary vaccination in later childhood or adult life. Also, the earlier the vaccination of the individual the higher is the general level of communal immunity.

The vaccination acceptance rate for England and Wales in 1957 for infants under the age of one year was 43 per cent. The rate has been increasing in recent years and is now a little above the rate before the repeal of the Vaccination Acts and much above the rate immediately following that repeal. About 70 per cent. of all primary vaccinations are done during the first year of life and 12 per cent. at age 1 to 4 years.

Like the other usual immunization procedures, smallpox vaccination is primarily the duty of the family doctor. Much immunization is done by medical officers of health and their staffs because they have the facilities for mass immunization, and also because in some areas the acceptance rate would otherwise fall alarmingly. Every possible opportunity should be made and taken to provide the necessary immunization in general practice. The value of vaccination against smallpox would be most obvious, and disastrously so, if the disease again became epidemic in this country as it would if vaccination fell largely into disuse.

CONTRAINDICATIONS

(a) Generalized eczema or diabetes mellitus: there should be no primary vaccination, but if vaccinated in infancy there may be a case for revaccinating every five years to maintain immunity.

(b) Illness, feebleness, infected skin conditions: vaccination should be deferred.

(c) Bad nutrition or congenital syphilis in infants: vaccination should be deferred except possibly in face of an epidemic.

(d) Prevalence of poliomyelitis declared to be high by the medical officer of health for the area: routine vaccination should be deferred.

TIMING OF VACCINATION

When smallpox vaccination was the only common immunization procedure timing was not complicated as it is today by the competing and increasing claims of other forms of immunization. The usual time chosen was at age 2 to 4 months, the family doctor keeping in mind that on the one hand it was well to wait until feeding had been firmly established and that on the other it was wise to vaccinate while the infant was relatively passive. Parliament supported this view in 1853 by making vaccination mandatory within three months of birth and later decreed, in effect, that if a parent proposed to develop an inhibitory conscience about vaccination he had better do so within four months of the birth if his scruples were to be respected.

Now, however, programmes for immunization have to be considered. If need be diphtheria immunization can well wait until towards the end of the first year; the second year is soon enough for tetanus toxoid if given at all. Whooping-cough appears often in early infancy, so that whooping-cough vaccination should not be delayed for any other kind of immunization or for any kind of administrative convenience such as that provided by the use of combined antigen. As early as possible in the second month appears to be the optimum time for starting the whooping-cough course. Earlier than this is too early for smallpox vaccination because of the desirability of maintaining a safe time-gap between vaccinations.

The Wellcome Foundation symposium on immunization in childhood (1959) recommended alternative schedules A and B as immunization programmes. If either of these, or indeed some other programme, is used it might be found convenient to fit in smallpox vaccination in the fifth or sixth months after whooping-cough vaccination but before poliomyelitis vaccination starts, but in any case with intervals of at least four weeks before and two weeks after any other immunizing procedure. Alternatively, smallpox vaccination may be delayed to a suitable space in the selected programme towards the end of the first year; failing this the second year or any time thereafter up to five years of age would be quite suitable for the protection of the individual. From the point of view of the public health, however, the first year is to be preferred to later years and in practice the longer the

deferment the greater is the risk of vaccination not being done at all.

Ideally, revaccination should be carried out as a routine every five years, but in this country and in present conditions it should be sufficient to revaccinate once during school life with further vaccinations in the light of the needs of travel and compliance with regulations in relation to duty or employment.

METHOD OF VACCINATION

The arm is clearly the best site for vaccination because of the smaller risk of severe reactions there than is the case in buttock, thigh or calf. The only

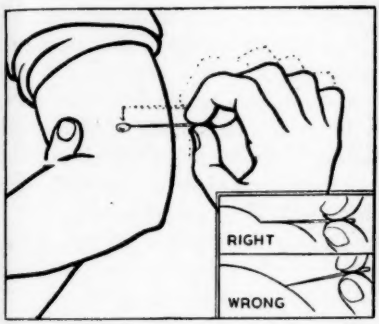

FIG. 1.—The 'multiple pressure' method of vaccination, showing the rapid up-and-down motion of the side of the needle, held by the hand at the right, against the drop of vaccine on the arm at the left.

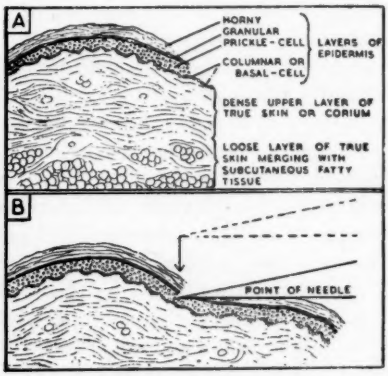

FIG. 2.—(a) Diagrammatic section of the skin of the arm. (b) Same, showing the motion of the needle from its first position above and parallel to the skin (indicated by the dotted outline) to its final position pressing against the surface of the skin and entering it slightly.

(Reproduced from 'Memorandum on Vaccination Against Smallpox', 1956, by permission of the Controller of H.M. Stationery Office.)

objection to the arm as a site appears to be cosmetic but the modern tendency for clothing to retreat from the periphery makes this objection correspondingly less valid. Soap and water are enough to make the site clean—and that is all that is needed. Some practitioners use acetone or ether, allowing complete evaporation before vaccination. Slowly evaporating antiseptics should not be used at all. Vaccine should be expelled by means of air expressed from a piece of rubber tubing of suitable calibre or from the teat of a feeding bottle. The vaccine should not be blown out because of the risk of contamination of the vaccine and also because vaccinia of the lip would be unpleasant for the vaccinator. Some doctors protect the vaccination lesion with a dressing, some do not. A light dressing is necessary if

the patient is dirty or likely to be. If the lesion develops the appearance of an infected wound it should be treated as such.

Single scratch method.—This method, recommended by a Ministry of Health Committee (1928), is still performed by many experienced practitioners because they feel that failure to take is less likely than in multiple pressure. It is also quicker: one scratch takes less time than ten to thirty or more pressures. For the same reason there is less discomfort and, in the case of a baby, time is particularly important because he objects at least as much to restraint as he does to clinical interference. It has been suggested in favour of the single scratch method that the resultant lesion and subsequent foveation can be minimal by this method. This is true but it should be remembered that too little foveation may also mean too little immunity. Scarification is performed with a sterile Hagedorn needle through the vaccine which has been applied to the arm. The scratch should be about $\frac{1}{8}$ to $\frac{1}{4}$ inch (3 to 6 mm.) long and very little experience is needed to achieve an effective one without drawing blood.

Multiple pressure method.—Lateral pressures are applied to the skin through a drop of vaccine with a sterile Hagedorn needle (fig. 1, 2): 30 for infants, 10 for other primary vaccinations and 30 for re-vaccinations, but the number of pressures is probably unimportant if they are made firmly, short of drawing blood. The area covered should be about $\frac{1}{8}$ inch (3 mm.) in diameter. It is claimed for this method that it has the least risk of sepsis —a claim similar to that in favour of single scratch. It is probable that there is no difference between the two methods in this respect if properly carried out. The exponents of multiple pressure claim also a higher number of takes from this method, but personal experience suggests that the single scratch method is superior in relation to this.

INTERPRETATION OF LESIONS

Primary take.—Results of vaccination may be read on the fourth day (papule), the sixth day (vesicle) and the tenth day (pustule), but variations do occur. The scab separates about the twenty-first day.

Vaccinoid.—This is an accelerated reaction in the partially immune. The scab separates in about eight days, the intervening stages being shorter and milder.

Immune reaction.—Papule which disappears within three days.

COMPLICATIONS OF VACCINATION

There is virtually no danger from smallpox vaccination if proper precautions are taken. Complications are now extremely rare. In 1957, in England and Wales 425,000 primary vaccinations were made and three deaths from generalized vaccinia were reported; two of them were of infants with congenital blood defect and one was associated with 'an exacerbation of pre-existent eczema'. An authoritative American opinion is that reports of

generalized vaccinia may be due to mistaken diagnosis. There were also two fatal cases of post-vaccinial encephalomyelitis in this country in 1957. Histological examination of the brain of one of these cases, an infant, was completely negative. The other case, re-vaccinated 49 years after vaccination in infancy, showed histological evidence characteristic of encephalomyelitis. Thus, to be weighed against the prevention of an untold number of cases of smallpox there was one death probably attributable directly to vaccination—out of a total of more than 500,000 vaccinations in 1957. Assuming 50 vaccinations each year by a family doctor he would on this basis expect to meet serious trouble from vaccination once in 10,000 years.

IMMUNITY PRODUCED BY VACCINATION

Immunity appears about the tenth day after vaccination. As the incubation period of smallpox is usually twelve days, it follows that full protection may be expected if vaccination is done within two days after exposure to smallpox. Within eight days protection is possible and attenuation of the severity of attack probable, but it is unwise to promise any protection. The duration of immunity varies enormously: probably from two to ten years for a primary take. Re-vaccination extends immunity almost indefinitely but should never be relied upon as complete. All persons who have been exposed to infection should be vaccinated unless vaccinated or re-vaccinated within the previous year.

ANTIVACCINIAL GAMMA-GLOBULIN

Peirce and his colleagues (1958) suggest that immune gamma-globulin prepared from recently vaccinated people may modify smallpox if given during the incubation period. Further experience is needed but it would appear that a practical application could be to vaccinate smallpox contacts and give gamma-globulin at the same time.

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DIPHTHERIA IMMUNIZATION

By W. POWELL PHILLIPS, O.B.E., M.R.C.S., L.R.C.P., D.P.H.

Medical Officer of Health and Principal School Medical Officer, Cardiff; Lecturer in Preventive Medicine, Welsh National School of Medicine

DIPHTHERIA as a common infectious disease has virtually disappeared from this country. This dramatic and outstanding success of modern medicine has not been achieved without a great deal of effort on the part of the laboratory workers, who have provided effective antigens, and those who have carried out the clinical administration of the protective materials. It is now important to maintain the position which has been reached. This can only be done by persistent work, which must aim at providing diphtheria immunization in a safe and convenient form so that the public will accept this protective measure as an almost routine procedure; even without the stimulus of severe diphtheria cases to arouse interest. The responsibility of convincing parents of the persisting need to have their children protected rests with the family doctor and his colleague in the public health service.

EPIDEMIOLOGY OF DIPHTHERIA IN RELATION TO IMMUNIZATION

The death rate for diphtheria has shown an almost unbroken decline from the beginning of this century (fig. 1). The notified cases, available from 1911 onwards, never fell below 40,000 cases per annum up to 1940 (fig. 2). In 1941, the Government sponsored national propaganda to secure mass immunization of children. This was directed particularly towards the pre-school child. The result has been that extremely few practitioners, who have qualified within the last decade, have seen a clinical case of diphtheria. It is interesting to note that this is no new experience.

Thomson (1951), when he reviewed the history of diphtheria immunization, drew attention to a historical fact of some significance. Sir John Simon wrote in 1858: 'Diphtheria is a disease which (though it has been experienced in former times) is well-nigh unknown to the existing generation of British medical practitioners'. It must be remembered, however, that there are varying types of diphtheria organisms and a type producing mild infection may well have been prevalent at the time when this observation was made. No means of bacteriological confirmation of diagnosis was available and notification was not practised. Later in the nineteenth century diphtheria assumed grave proportions as an infection with a high mortality.

The dramatic fall in notifications and deaths from diphtheria since 1941 is due to two factors: (1) the high rate of active immunization, both for children of pre-school and school age, and (2) the efficiency of the prophylactic antigens which have been used. Greenberg (1955) has shown that a protection rate of at least 70 per cent. is required to prevent the spread of the disease in the community. This has been the experience both in this country and in North America. Diphtheria may well occur when the level

of herd immunity is permitted to fall below approximately 70 per cent. of the child population. It may occur even among those who have been immunized.

As an example, there were 561 diphtheria patients in the Cardiff City

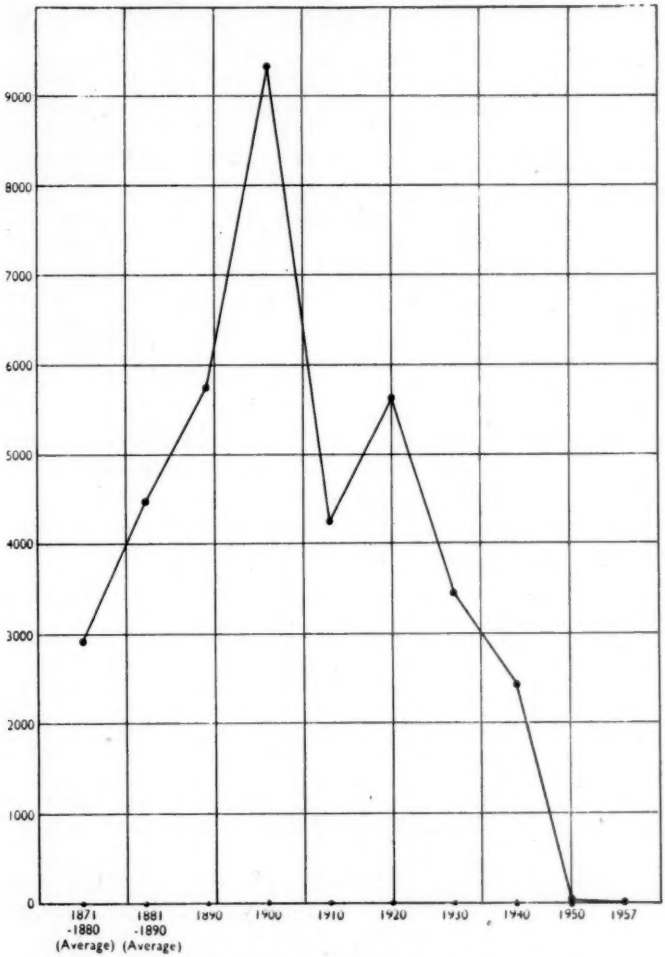

FIG. 1.—Diphtheria deaths in England and Wales, 1871-1957.

Isolation Hospital in the year 1937. Of these, 74, or 13 per cent., had been immunized previously. At this time some 50 per cent. of the child population in Cardiff were protected, but a significant fact was that the number of pre-

school children protected was much below the average for children of all ages.

This is in no way intended as an argument against the efficiency of immunization but rather to stress the necessity of having a high protection rate among the children of pre-school and school age. Ipson and Bowen (1950) draw attention to the fact that the adult population is no longer sub-

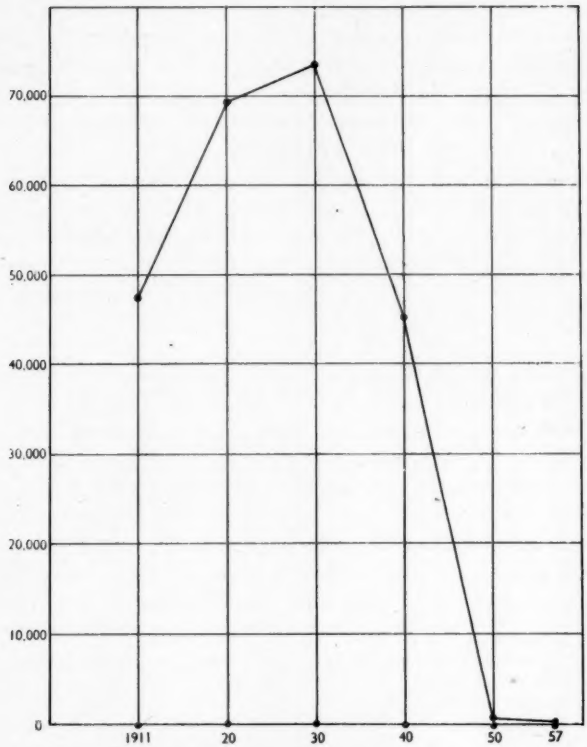

FIG. 2.—Diphtheria notifications in England and Wales, 1911-1957.

ject to subclinical infection which formerly acted as a booster to acquired immunity. However this may be, the practical fact remains that experience has so far shown that a high rate of protection in pre-school and school children appears to maintain the immunity of the human herd. Should there be a reappearance of diphtheria it may become necessary to consider the immunization of adults, but at present this is not considered as a requirement save for those who may encounter a special risk from the nature of their employment.

That protective methods are still important is shown by O'Herlihy (1957). During 1957, 60 clinical cases of diphtheria were admitted to the Dublin Fever Hospital with a 10 per cent. mortality. The predominant strain of organism in the fatalities was the gravis type. In view of the proximity of infection of this nature it is essential to maintain herd immunity at a high level.

The Ministry of Health now compile a return which does serve to indicate the measure of protection attained for children under the age of 15. This is known as the immunization-index. The present position, with an immunization-index of 46.7 per cent. for England and Wales, does not permit of complacency, but should give rise to increased effort on the part of the medical profession. There is a risk that, if there is a failure to appreciate the importance of active immunization on the part of the public, diphtheria may return in a virulent form. Without the stimulus of naturally occurring infection there is the danger that diphtheria organism may find a sufficient quantity of susceptible hosts to produce localized or nation-wide epidemics before our methods of control through active immunization can become effectual.

COMPLICATIONS OF DIPHTHERIA IMMUNIZATION

It is perhaps unusual to discuss the complications of a procedure before describing the procedure itself. It is brought forward because of the fact that the actual complications encountered have an effect upon the selection of the materials to be used in immunization against diphtheria.

McCloskey (1950), Martin (1950) and Geffen (1950) independently showed that paralytic poliomyelitis sometimes occurred following the injection of diphtheria prophylactics, both when used as a single antigen and in combination with whooping-cough vaccine. The incidence of paralysis was higher in the limb which had received an injection, usually within a period of twenty-eight days before the onset of the symptoms of poliomyelitis. This has given rise to intensive investigations to discover the cause of this complication and also, if possible, to eliminate or minimize any likely risk of its occurring. It is considered that the poliomyelitis virus becomes localized in the anterior horn cells supplying an area which has received a provocative injection. No evidence has been brought forward to suggest that the virus is introduced with the antigen at the time of injection. If this were the case it would be expected that groups of cases would arise in relation to a particular series of injections. This has not occurred. It is presumed that during a period when poliomyelitis is prevalent in the community the injection acts as a provocative in an individual who is exposed to the poliomyelitis virus. In some manner the injection may localize an infection which otherwise would have remained subclinical. Bousfield (1951) has suggested that subcutaneous inoculation will reduce the effect of local trauma. The whole problem of poliomyelitis following injections against

diphtheria and whooping-cough was the subject of a report by a Medical Research Council Committee (1956). As a result of this report it was concluded that preparations containing alum as an adjuvant to the toxoid carry an increased risk of poliomyelitis as a complication. This was also considered to apply to diphtheria toxoid combined with whooping-cough vaccine. It was not considered that subcutaneous injections had any effect in lessening the danger of the complication.

Apart from the rare hazard of a provocative poliomyelitis there are relatively few complications to diphtheria immunization. As with any procedure which breaks the continuity of the skin, infection may be introduced. A sterilized syringe and needle should be used for each injection. Reaction due to the protein content of the injected material becomes more troublesome as children increase in age. In infancy any local or general reaction is rare apart from the fact that a small nodule of fibrosis may be just palpable under the skin and usually leads to an inquiry by the mother. This is a common reaction and will disappear after a period of two to three months. Sometimes, but with extreme rarity, the nodule will break down and discharge a small quantity of pus. Experience has shown that such abscesses are sterile on culture. In older children, from 10 years upwards, and in adults, a quite intense local and general reaction may follow immunization. The arm may become swollen, painfully hot and tender from the shoulder joint to below the elbow when the injection has been given into the arm. These signs are accompanied by malaise and pyrexia which may incapacitate a patient for a week but usually subside within seventy-two hours.

When considering the complications of diphtheria immunization it is only the risk of provocative poliomyelitis which requires consideration when making a decision as to a planned programme of immunization. No child should be permitted to reach the age of one year without diphtheria prophylaxis, provided the injections are given when the child is well. This is stated merely because any complication of the illness would be attributed to prophylactic injection if this were administered when the child was not fit. Questions are often put as to whether a child who suffers from the various signs of allergy, such as asthma or eczema, is a suitable subject for diphtheria prophylaxis. These symptoms are not a contraindication.

PRACTICAL APPLICATION

The most potent antigens, when judged by the Schick test conversion-rate, and also by estimations of the antitoxin content of the serum, are the diphtheria toxoids which are precipitated or adsorbed with alum. To a large extent it was these preparations which were used at the time of the mass diphtheria immunization campaign of 1941 and onward. Unfortunately these effective antigens cannot be recommended for use today because they are incriminated as inciting agents in provocative poliomyelitis. This also applies with greater force when they are combined with whooping-cough

vaccine in a double antigen preparation and probably if used in combination with both tetanus toxoid and whooping-cough in a triple antigen.

Purified diphtheria formol toxoid (D.T.), when given alone carries no special risk of inciting poliomyelitis. Opinion is divided as to whether or not there is a danger when diphtheria toxoid is combined with whooping-cough vaccine as a double antigen or with whooping-cough vaccine and tetanus toxoid as a triple antigen. Many general practitioners may consider that by the administration of multiple antigens they are more likely to receive the cooperation of parent and child. Certainly in the United States, Canada and Australia the immunization schemes are almost wholly carried out by the use of multiple antigens and all of the facts relating to the possibility of paralytic poliomyelitis have been considered in their reports on this subject. A balanced view has to be maintained as to whether or not the patient will accept treatment if it is not provided with the minimum discomfort to the child. The rare occurrence of poliomyelitis arising as a complication has to be judged against the risk of diphtheria recurring in much the same proportions as it did before the era of immunization.

Diphtheria toxoid when used without whooping-cough vaccine is not a very potent antigen, but when combined with whooping-cough vaccine it is as effective as the alum preparations. It is the whooping-cough vaccine which has an adjuvant effect upon the diphtheria toxoid and increases its efficiency. The addition or otherwise of tetanus toxoid does not influence this factor.

For the primary immunization of children in infancy a decision has to be made whether or not to give diphtheria toxoid alone, in which case two injections are required. These are given at any time after the first three months of life and before the age of twelve months. An interval of at least four weeks must be allowed between these two doses. The amount to be given is 1 ml. of diphtheria toxoid for each injection. If it is desired to immunize against tetanus with tetanus toxoid, this antigen can be given mixed with diphtheria toxoid and incorporated in the same actual quantity of material, namely, 1 ml. Should this plan be adopted, a recall single dose of 1 ml. of either diphtheria toxoid or diphtheria toxoid and tetanus toxoid should be given eighteen months after the last primary injection was given.

Should it be decided that whooping-cough vaccine is to be given mixed with the diphtheria antigen, then three injections, the first administered when the child is three months old and then at monthly intervals, should secure a sound basic immunity. Tetanus toxoid may also be combined. Again the usual dosage is 1 ml. for each injection. To preserve a sound immunity against tetanus one further injection after eighteen months will be necessary. It will thus be seen that, if it is desired to immunize against both diphtheria and whooping-cough, a combination of antigens does reduce the number of injections required.

The age at which diphtheria immunization is best carried out depends

upon whether or not it is used in combination with whooping-cough vaccine. The whooping-cough vaccine, in order to be effective in the control of this disease in the young child, must be given as soon as possible, and the age of three months is suggested because by that time the infant should be progressing satisfactorily and his immune mechanism should have developed sufficiently to utilize the antigen. Should diphtheria toxoid be given alone, then the child must be protected by the time he is twelve months.

A child who has been actively immunized during infancy requires a further stimulus at the age of approximately five years, when entering the more varied environment of school life. School entrants should therefore be stimulated further by the injection of a single dose of diphtheria antigen, 1 ml. Reactions to the toxoid, both of a local and general type, may occur at this stage, whereas they are extremely rare in infancy. For this reason toxoid-antitoxin floccules (T.A.F.) is a convenient alternate material to use, as it rarely gives rise to a severe reaction. The dose is similar to that recommended for diphtheria toxoid.

Finally, at the age of ten years a further check should be made to ascertain whether or not the child has a satisfactory grade of immunity. Diphtheria antigens at this age are particularly prone to give rise to quite severe reaction, especially in those who are negative or pseudo-positive reactors to the Schick test. For this reason it is well to use the Schick test and control test before any prophylactic antigen is given. The relatively small number of Schick-positive cases should then be given a single dose of 1 ml. of T.A.F.

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PERTUSSIS VACCINATION

By W. CHAS. COCKBURN, M.B., M.R.C.P., D.P.H.
Director, Epidemiological Research Laboratory,
Central Public Health Laboratory, London, N.W.9

No bacterial vaccine has been tested more comprehensively in the field and in the laboratory than pertussis vaccine. Studies in this and other countries have shown conclusively that a good vaccine will prevent or modify the disease in the vaccinated for at least three years after the primary course. They have also shown that vaccines which give good results in the intracerebral mouse challenge test in the laboratory give good protection in children. A standard vaccine has now been prepared against which new batches of vaccine can be tested in the laboratory. Vaccines as good as the standard may be relied upon to reduce the attack rate in children exposed to infection by their siblings from about 85 per cent. to 30 per cent. or less, and to modify the severity of the disease in those not fully protected.

Although pertussis vaccine is not yet issued free of charge to local authorities, nearly every local authority has obtained permission to prepare schemes for pertussis vaccination. In many areas medical officers of health and family doctors have been using it for years. In some of these areas observations show that the incidence of pertussis in the youngest age-groups, in which vaccination is most widely used, is beginning to fall more rapidly than in the older children. A fall is also appearing in the national notification figures. Between 1948 and 1954 the average annual number of notifications was about 135,000. Between 1955 and 1958 it dropped to 72,000. The fall may be due to vaccination or to some natural variation in incidence, but proportionately the fall is greatest in children between one and four years of age, the period when vaccination is commonest.

AGE OF VACCINATION

In planning how to use to the best advantage an active immunizing agent against any disease account has to be taken of the age at which most cases occur and the age at which most deaths occur. In pertussis the peak of morbidity and the peak of mortality are at different ages.

Of the *cases*, about 9 per cent. are in children below one year of age; between 9 and 12 per cent. occur in each of the next four years, so that about 55 per cent. are in the first five years. About 40 per cent. are in children between five and nine years of age and the remainder are in older children. Most children therefore develop pertussis in the pre-school period. In contrast, nearly four-fifths of the *deaths* are in children less than one year old, and nearly half are in children less than six months old. The number of deaths is falling rapidly. From 1948 to 1954 the average number each year was about 375. From 1955 to 1958 it was about 70 and for 1958 alone it was

less than 30. If deaths continue to fall it may soon be possible to discount the risk of death and to vaccinate about the end of the first year to ensure the child's immunity being high when the incidence is high. At present, however, deaths have still to be taken into account and vaccination should be carried out as early as possible in a child's life. The child's capacity to produce antibodies in response to the antigenic stimulus of the vaccine is not as great in the first few months of life as later, but there is evidence of protection from early vaccination. A dose of vaccine therefore should be given at the beginning of the second, third, and fourth months. A reinforcing dose should be given between the 12th and 18th month. If it is necessary to reduce the number of injections to the minimum the third dose (at the beginning of the fourth month) might be omitted. The chance of a child developing pertussis below six months of age is very small. What has to be guarded against is the risk of the child dying if he does develop the disease. Two doses of vaccine would probably do this. No matter whether two or three injections are given in the primary course another dose should be given between 12 and 18 months of age.

SCHOOL ENTRY

More time must elapse and more experience be gained before it will be possible to say whether children not previously vaccinated should be given a primary course at school entry or whether children who were fully vaccinated in infancy should be given a reinforcing dose on entering school. If it is shown, as some early observations suggest, that in children immunized in infancy immunity wanes at about five years of age there may be a demand for a reinforcing dose then. But postponement of the disease for another few years may not be wise. Except in the most unusual circumstances there are no deaths from pertussis in children of five or more years of age and there is little evidence of serious complications. It may therefore be advisable not to try to prevent children developing the natural disease about this time. If they do become infected they will probably have a modified attack provided they were vaccinated in infancy, and will acquire a lifelong natural immunity.

THE TYPE OF VACCINE

In Britain excellent results have been obtained by using a whole bacterial vaccine grown on solid or in liquid medium, killed with 'merthiolate' or formalin, suspended in saline, and preserved with merthiolate. The vaccine is usually given in 3 doses of 1 ml., each containing 20,000 million organisms, at one-month intervals. Alum has occasionally been added to this type of vaccine because it enhances the production of agglutinins in children below six months of age. There is evidence, however, that agglutinin production does not necessarily indicate the degree of protection afforded by a vaccine. The addition of alum increases the risk of local reactions, abscess formation, and provocation poliomyelitis so there is at present little to

justify it. The investigation of antigenic fractions of the pertussis bacillus holds greater promise for the future. One soluble fraction has already been shown to give as good or better protection than a whole bacterial vaccine. Such a fraction which contains very little bacterial protein might be of great value in the future, particularly in mixed antigens.

REACTIONS

In a recent study of children six to 24 months old the proportion with reactions rose from near 50 per cent. after the first injection to about 75 per cent. after the third injection, but parents did not consider the reactions as contraindications to completing the full course. It was difficult to find a satisfactory method for measuring the degree of general reaction but the size of the area of redness and swelling of local reactions was measured and it was found that in three-quarters to four-fifths of the cases the area of local reaction was less than 5 cm. Local and general reactions with whole bacterial vaccines not containing alum are therefore not serious.

Encephalopathy.—In the past twenty-five years over 100 cases of convulsions and coma, sometimes going on to hemiplegia and mental deterioration or death, have been reported after the injection of pertussis vaccine. At least seven serious cases have occurred in the United Kingdom. Although some were probably unconnected with the vaccine and occurred by chance soon after the injection, most were unquestionably precipitated by the injection. They occurred nearly always within twenty-four hours after an injection and more than half occurred within six hours after an injection. They have been reported after every type of pertussis vaccine used on a large scale and have been precipitated by any of the injections in a course. About half the patients have made a complete recovery, about one-third have had serious permanent neurological lesions and about one-sixth have died. The pathogenesis is unknown. There is some doubt whether a previous history of central nervous system lesions in the vaccinated child or in his immediate family is a predisposing factor, but there is no doubt that if a neurological reaction has been observed after one injection a subsequent injection is likely to precipitate another and probably more severe reaction. A child therefore who has a neurological reaction, however mild, should on no account be given further injections. In the present state of understanding of encephalopathy it is probably wise also not to vaccinate a child with a personal or family history of central nervous system disease, or a child who is ill or is convalescing from an illness.

The risk of encephalopathy after vaccine, though real, is so small that it is not possible to estimate it accurately. Whooping-cough itself also may cause lesions of the central nervous system as well as serious respiratory complications and death, especially in the very young. Even an uncomplicated attack in a baby is distressing, prolonged and severe. While the incidence of pertussis is high there is every justification for pressing on with vaccination. There is, however, need for a serious effort to be made to

obtain full details of every case of encephalopathy which occurs in this and other countries and to study the properties of the component parts of the pertussis bacillus in the hope that either the vaccine can be made entirely safe or the potentially susceptible children can be recognized before they are inoculated.

MIXED VACCINES

So far pertussis vaccine has been considered alone but it is often mixed with diphtheria toxoid or with both diphtheria and tetanus toxoids. By giving three antigens in one injection the number of injections is reduced. There is therefore a great advantage in using mixed antigens, but there are also disadvantages. As pertussis vaccine has to be given below 6 months of age the toxoids in mixed antigens are administered when the antitoxin response to them is poorer than it would be if the child were a few months older. This poor response can usually be overcome by giving an additional dose either as part of the primary course or as an early reinforcing injection. The main disadvantage of mixed antigens is their tendency occasionally to provoke the onset of paralytic poliomyelitis, often with paralysis in the injected limb. A recent report has shown that one case of provocation poliomyelitis may occur in every 20,000 injections. When the antigens are given separately this risk is absent or much reduced. If poliomyelitis vaccine could be given before mixed antigens the risk of provocation poliomyelitis might be removed, though this is by no means certain. Unfortunately, the response to poliomyelitis vaccine below six months of age is very poor and this possible way of avoiding the risks with mixed antigens is not open.

SUMMARY

A plain suspension of killed pertussis bacilli in saline given in three doses, each of about 20,000 million organisms, will give good protection against whooping-cough for at least three years.

Children should be vaccinated as early in life as possible and should be given a reinforcing dose at 12 to 18 months. It may be wise not to give further reinforcing doses but to allow a child to develop a natural immunity when the artificial immunity wanes.

Local and general reactions are not severe.

Encephalopathy is a very rare risk but very serious when it does occur. Its pathogenesis is unknown. A child who shows any sign of a neurological reaction should never be given further injections of pertussis vaccine, as there is a strong possibility of a severe recrudescence of the reaction. Children with a personal or family history of central nervous system lesions should probably not be vaccinated at all, nor should children be vaccinated when they are ill or are convalescing from any disease.

Mixed vaccines containing diphtheria toxoid, tetanus toxoid and pertussis vaccine are commonly used and have obvious advantages, but they carry a greater risk of causing provocation poliomyelitis than do these antigens when given separately.

TETANUS IMMUNIZATION

By LESLIE COLE, M.D., F.R.C.P.
Senior Physician, Addenbrooke's Hospital, Cambridge

It is a paradox that with two practical methods of producing immunity against tetanus, prevention still presents problems. This article is an attempt to discuss the difficulties which arise and to consider how they should be met.

The problem of clinical tetanus in England and Wales is a diminishing one as is shown by the Registrar General's Statistical Review. In 1947, there were 71 deaths (49 males and 22 females) and in 1957 there were 28 (23 males and 5 females). Assuming there is one fatality in every three, which is probably an over-estimate, there would have been approximately 213 cases in 1947 compared with 84 in 1957.

ETIOLOGY AND PATHOLOGY

Clostridium tetani is an anaerobic spore-forming organism which on germination in the tissues produces a neurotoxin. This reaches the spinal cord via the axis cylinders and produces clinical tetanus. The organism is common in soil, particularly in agricultural districts, and is found in the excreta of man, horses, cows, sheep and other animals. Unless prevented by immunization, tetanus is likely to occur when the organism is introduced deeply into the tissues where it can germinate in the absence of oxygen. Its growth is facilitated by concomitant pyogenic infection and the presence of foreign bodies and necrosed tissue. Tetanus spores are highly resistant, so that many substances used in medicine may become infected if there is any laxity in sterilization. Many of these are listed in a recent M.R.C. report (1959) and include catgut, gelatin, glue (bunion pads), court plaster, powders such as talc, starch, fuller's earth, vaccines, antisera, cellulose wadding, brown, grey or unbleached cotton-wool, plaster of Paris bandages and dust or wall plaster. The danger from contaminated gloves is also stressed. Such considerations indicate the type of wound which is most likely to cause tetanus and explain the rare occurrence of cases from unexpected sources or when no wound can be found. It is these odd examples which make the problem of complete prevention so difficult.

In this country deep infected wounds rarely cause the disease because in these it is prevented by routine passive immunization. Instead it usually occurs after relatively mild injuries which are not taken to a doctor or, if so, are not considered severe enough to need antitoxin. Thus, in a series of 43 consecutive cases of tetanus seen at Addenbrooke's Hospital between 1928 and 1939 (Cole, 1940), nine were due to dirty abrasions which had scabbed over, 12 to slight penetrating wounds and nine to whitlows. In 11 others the lesions were varied and included burns, chronic ulcers, otitis media, impetigo, puerperal infections, umbilical sepsis in the newborn and

in two no wound could be found. These are a representative sample from an agricultural district. It cannot be too strongly stressed that uncleanliness is an important etiological factor. If infection in a wound could be eradicated sufficiently thoroughly and quickly by local measures clinical tetanus could be prevented, but this is not possible.

Man has no natural immunity to tetanus and immunity is not conferred by an attack. Two methods are available for preventing the disease: (1) passive and (2) active immunization.

PASSIVE IMMUNIZATION

Passive immunization can be produced in man by administering antitoxin from a horse which has been actively immunized by injections of toxoid and later toxin. This antitoxin does not influence the organism in the wound but neutralizes toxin as fast as it is formed before it can gain access to nerve cells. Once toxin has become 'fixed' to nerve cells it cannot be affected by antitoxin, so it is important to give antitoxin as soon as possible after wounding. After all wounds from which tetanus might arise 1,500 international units (I.U.) or, with severe wounds, a larger dose should be given subcutaneously or intramuscularly without delay. The protective effect reaches its maximum in two to three days and then passes off gradually in about a fortnight. It is important to remember this evanescent effect and to repeat the dose at weekly intervals in heavily infected wounds which might continue to produce toxin. The value of passive immunization was first proved conclusively in the 1914-18 War. Its introduction in 1914 as a routine for all wounded reduced the incidence of tetanus from 0.9 to 0.1 per cent. in a few months and its effectiveness has since been confirmed (War Office Committee, 1917, 1919). It is now accepted that prophylactic antitoxin, if given at once, greatly reduces the likelihood of tetanus. If it fails to protect, the disease usually occurs in a benign form with a long incubation period and often local tetanus—the latter a good prognostic sign—and most patients recover. Among civilians, if prophylactic antitoxin is given within twenty-four hours of wounding the disease is rarely fatal.

The chief disadvantages of passive immunization are:—(1) The temporary nature of the protection afforded. (2) The fact that a second dose may give less effective protection than the first. (3) The liability to serum reactions, particularly in allergic subjects and those who have previously received an injection of horse serum. Too much should not be made of these disadvantages, for passive immunization is a valuable protection against tetanus. Cases due to slight wounds or bizarre causes must inevitably slip through the net of passive immunization but if sensibly used it is of great protective value and its risks are relatively slight.

It cannot be too strongly emphasized that a doctor should give prophylactic antitoxin at once after all wounds in which he considers there is the slightest possibility of tetanus infection but the final decision as to whether to give it must rest with him.

SERUM REACTIONS

In giving prophylactic antitoxin it has to be remembered that the injection of horse serum is liable to be followed by various reactions, particularly in allergic subjects or those who have received it previously. Because of this risk a careful history should always be taken with these points in mind so that precautions can be taken. Reactions vary from immediate anaphylactic shock, characterized by pallor, breathlessness and collapse, to delayed manifestations of serum sickness such as urticaria, œdema, joint pains and pyrexia, which usually develop after five to ten days. Local reactions also occur but these are seldom serious.

As a precaution against such reactions Parish and his colleagues (1957) recommend that a syringe of 1:1000 adrenaline should always be in readiness for emergency use when antitoxin is injected and that the patient should be kept warm and under observation for at least thirty minutes after it has been given. If there is no history of allergy or previous serum injections, they recommend that the whole injection of antitoxin may be given subcutaneously without delay. If there is a history of a previous injection of serum but none of allergy, 0.2 ml. of undiluted serum should be given and if there is no general reaction in thirty minutes a full dose of 1,500 I.U. If there is a history of allergy, a trial dose of 0.2 ml. of a 1:10 dilution of antitoxin should be given subcutaneously. If there is no general reaction in thirty minutes, 0.2 ml. of undiluted antitoxin should be given and if there is again no reaction in the next thirty minutes the full dose should be given. If there is a reaction the trial dose of 0.2 ml. of undiluted antitoxin should be repeated after the blood pressure has become normal and rashes have subsided—usually in six to twelve hours. If no general reaction occurs after thirty minutes the full dose should be given. Precautions on these lines should always be taken if there is any reason to anticipate reactions or if for any other reason, such as intercurrent disease, an unexpected reaction might be especially serious. Reactions should be treated by subcutaneous injections of adrenaline, antihistamines and general measures for shock. For severe cases a noradrenaline drip may be necessary and occasionally steroid therapy provided there are no contraindications. They emphasize that the object of a trial dose is to determine any predisposition to general reaction and not to detect any local reaction.

Laurent and Parish (1952) have shown that intradermal tests for sensitivity are unreliable, and Moynihan (1956) has also produced evidence in support of this view.

ACTIVE IMMUNIZATION

In 1933, Leavitt showed that man also could be immunized by injections of formol toxoid. A single injection produces little antitoxic response but subsequent injections after an interval of at least four weeks produce a gradual rise in titre. In the 1939-45 War this method was used as a routine for all British (Boyd, 1946) and American (Long and Sartwell, 1947)

troops before going on active service. Two injections of 1 ml. of formol toxoid were given at an interval of four to six weeks, followed by a similar boosting dose at yearly intervals while serving. If a wound were incurred procedure varied in the two armies. The British favoured passive immunization and antitoxin was given after wounding because it was argued that active immunization takes some time to develop; the Americans relied entirely on active immunization and after wounding gave a further dose of toxoid only and no antitoxin. Both these alternatives reduced the incidence of tetanus to negligible proportions. Active immunization alone has the advantage that it will usually protect without medical intervention at the time of wounding and because toxoid never produces more than mild reactions.

IMMUNIZATION IN CIVILIAN LIFE

The problem which confronts a doctor in civilian life is often not an easy one. If the whole population were actively immunized in childhood and maintained by boosting doses it would only be necessary to give toxoid if a wound were sustained more than a year after the last boosting dose. While active immunization remains a casual procedure—as in this country—toxoid can only be given with confidence after wounding if the doctor is sure that the patient has been actively immunized in the past and his immunity has still been maintained by boosting doses. If, as is usual, he cannot be certain of this, then his only alternative is to give passive immunization at once and arrange to give active immunization a few weeks later when the need for immediate protection from passive immunization has passed. This will ensure that, if his patient sustains another wound, he does not have to rely on a second and probably less effective injection of antitoxin with further horse serum and greater likelihood of reaction. If active immunization were carried out as a routine after antitoxin many of the problems which arise from giving a second dose of horse serum would disappear.

At present in this country the majority of civilians are not actively immunized against tetanus so the population may be conveniently divided into three groups: (1) Those who are actively immune at the time of wounding; that is to say, they have been actively immunized by three injections of toxoid properly spaced and subsequently maintained by boosting doses at five-yearly intervals. (2) Those who have had active immunization which has not been completed or maintained with boosting doses and are therefore not immune at the time of wounding. (3) Those who have never been actively immunized. Patients in groups (2) and (3) need immediate passive immunization if they sustain a wound and an injection of 1,500 I.U. should be given without delay. This should be followed by active immunization immediately the need for passive protection has passed.

While active immunization of the whole civilian population is considered impracticable the question arises whether there are particular sections at

special risk. Conybeare and Logan (1951) have recommended that children, particularly those living in rural districts, should be actively immunized so that by the time they start school at five they are protected, and this is being carried out on a considerable and increasing scale. Boyd (1951) has recommended active immunization for all agricultural workers, grooms and others who work on the land and are at occupational risk. The question is often asked what steps should be taken to protect an individual or group of people considered to be at special risk: for example, a football team playing regularly on fields where horses graze. Active immunization is the only answer. It should also be considered for all allergic subjects and those who have received an injection of horse serum in the past so that complications from further injections are avoided. Finally, consideration should be given to patients with chronic ulcers or other infected lesions which are likely to take a long time to heal.

It must be clear from what has been said that, if a patient is to get full benefit from active immunization, his doctor must know what immunizing injections he has received, with dates. It is essential for every patient to be able to produce this information. Parish has recommended that a card should be issued to every patient when active immunization is given, and kept up to date. If a doctor does not know these facts he has no choice but to give passive immunization so that the patient gets the benefit of the doubt.

COMBINED IMMUNIZATION

Active immunization in children presents special problems because the immunization programme for the modern child is becoming rather a full one. Combined immunization against diphtheria, tetanus and whooping-cough is conveniently given in a single injection as triple antigen and has been extensively used. For primary immunization three doses of 1 ml. intramuscularly or deep subcutaneously are given between the second and sixth month, with a boosting dose at about the first birthday. Immunity to tetanus is maintained by a further injection of toxoid at five years of age when the child goes to school and again after some years but there is still some uncertainty as to how often it is necessary to give further injections to maintain complete protection.

The use of triple antigen is not free from reservations. A recent M.R.C. Report (1956), based on statistical evidence, shows that inoculation against diphtheria and whooping-cough combined is slightly more liable to provoke poliomyelitis than if each is given singly. By analogy the same effect might be produced by tetanus toxoid combined with other antigens. The Central Health Services Council has therefore advised that antigens should preferably be given separately, particularly during the second and third quarters of the year when poliomyelitis is more prevalent. The advantage of doing this must be weighed against the disadvantage of giving more frequent injections to children.

The problem of fitting tetanus immunization into a programme which

also includes immunization against whooping-cough, diphtheria, smallpox and poliomyelitis is complicated and the slight risk of provoking poliomyelitis by using combined antigens makes it more so. The answer is beyond the scope of this article but the recent Wellcome Foundation symposium on 'Immunization in childhood' (1959) discusses the problem in detail and makes recommendations. Two schedules are suggested: 'A' and 'B'. The former is designed to reduce such hazards as 'provocation' poliomyelitis to a minimum and the latter, by using triple vaccine, to reduce the number of injections and to produce useful protection at an early age against four important diseases of childhood including tetanus.

SUMMARY

The sources of infection and the types of injury likely to cause tetanus are discussed.

Passive immunization should be given at once after any wound in which the possibility of tetanus infection is suspected.

The steps which should be taken to avoid and treat reactions to horse serum are outlined.

Passive immunization should be followed by routine active immunization, thus obviating the risk of reactions to further horse serum at a later date.

Active immunization is the method of choice for preventing tetanus, and immunity should be maintained by boosting doses.

A patient known to have been actively immunized and maintained immune should be given toxoid if he sustains a wound. Otherwise he should be given antitoxin and then actively immunized.

All children should be actively immunized by the age of 5 years, as well as all adults who are at special occupational risk.

Every patient who is actively immunized must be given a card to carry, with details of the immunizing injections he has had and the dates.

The slight risk of provoking poliomyelitis by using combined antigens should be remembered.

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POLIOMYELITIS VACCINE

By H. J. PARISH, M.D., F.R.C.P.Ed.

Clinical Research Director, Wellcome Research Laboratories, Beckenham, Kent

THE poliomyelitis vaccines used in Britain are prepared according to the method of Salk. The greater part of this article will therefore be devoted to a consideration of what has come to be known as the Salk vaccine, with a concluding short section on live vaccines.

INACTIVATED VACCINE (SALK)

The Salk vaccine is a suspension of the three known immunological types of poliomyelitis virus, grown in monkey kidney tissue in synthetic medium and inactivated with formaldehyde. Although this chemical treatment has destroyed the ability of the viruses to cause disease, the vaccine retains its capacity to stimulate the production of antibodies to poliovirus.

Method of preparation.—The strains employed are: Type 1—Mahoney (in American and Canadian vaccines), replaced by modified Brunhilde-Enders or Brunenders (in British vaccines); Type 2—MEF—1; and Type 3—Saukett. Type 1 poliovirus is of special importance since it is responsible for about 80 per cent. of all paralytic infections. The immune responses evoked by the Mahoney and Brunenders Type 1 strains are of similar magnitude, but the latter has the advantage of relatively low virulence.

Small amounts of various antibiotics, which are added to the culture medium in order to prevent bacterial contamination, are removed to a variable extent during processing: they may be present in the final product.

Laboratory tests for safety and potency.—Technical knowledge and skill of a high order are essential as the processes of manufacture are most complicated. Large samples of vaccine are tested at repeated stages, both before and after the three types of virus are mixed. In addition to tests for bacterial sterility, the exclusion of living virus from the product is demonstrated by examination of very large volumes by tissue-culture techniques. A further safety test involves the injection of vaccine into live monkeys to which cortisone is administered in order to increase their susceptibility to poliomyelitis infection. Approximately three weeks later the animals are killed. No evidence of the disease must be observed during intensive histological examination of the brain and spinal cord at different levels.

The antigenic potency of each batch is assayed by vaccinating groups of monkeys, and testing the serum antibody content of each animal before and after vaccination. This is done by estimating the capacity of the serum to neutralize each of the three types of living poliomyelitis virus when added to monkey kidney cell cultures. Other species of animals, such as chickens, are being investigated for their suitability for tests of antigenic potency.

As a further check, duplicate tests for safety and potency are made by

the Medical Research Council, and great importance is attached to the consistency of the results with successive batches, as an indication that the safety of the routine processing is not marginal.

Storage and stability.—The vaccine will retain its potency for at least twelve months, when stored at 2° to 10° C. Exposure to ordinary temperatures for short periods during transit is not deleterious, but it is recommended that the vaccine should not be left unrefrigerated longer than seven days. Because of the rapid loss of potency above 30° C., poliovaccine should not be transported in the tropics without refrigeration.

DOSAGE AND INTERVALS BETWEEN INJECTIONS

The primary course should consist of the intramuscular or subcutaneous administration of three doses, each of 1 ml., with intervals of four to six weeks between the first and second doses and seven to twelve months between the second and third doses. The third dose, however, may be given as early as four to five months after the second, if there is an enhanced risk of infection because of the imminence of the poliomyelitis season, during pregnancy, or for some other reason.

Active immunity, with the formation of protective antibodies in the blood stream, takes some time to develop. For this reason, at least the first two doses of vaccine should ordinarily be given well before the end of May, when the incidence of poliomyelitis tends to increase in this country.

REACTIONS

Over 200 million injections of Salk-type vaccines have now been given in different parts of the world since the Cutter disaster of 1955, which has not been repeated. Complete safety has obviously been attained, and it is clear that there are no serious hazards. Moreover, the administration of vaccine has been remarkably free from reactions of all types, even in allergic subjects, so that a history of asthma or other allergy is not, by itself, a contraindication to injection. According to recent reports, persons highly sensitive to penicillin or streptomycin may be at special risk, and it is a wise precaution, as in the administration of all vaccines as well as antisera, to have adrenaline (1 in 1000) available for emergency use. Future vaccine will not contain penicillin. Apart from the rare allergic manifestations, other illnesses reported have probably been chance associations in time.

The user should observe the appearance of the vaccine, which should be perfectly clear and orange to cherry-red in colour due to the presence of a small amount of phenol-red indicator in the culture medium. Small variations in colour are of no significance, but vaccine which is yellow or has become turbid might cause troublesome reactions and should not be used.

RESPONSE TO IMMUNIZATION: DURATION OF IMMUNITY

Vaccination causes formation of circulating antibodies, which keep invading viruses from reaching nerve cells and causing paralytic poliomyelitis. Two injections of vaccine are likely to give 75 to 80 per cent. protection against the paralytic disease: and three injections over 90 per cent. protection. (The

incidence of 'non-paralytic poliomyelitis' is only slightly affected, but this is relatively unimportant as the patient is not left with a permanent handicap.) The duration of the protection obtained after three doses of vaccine is still under investigation; there is no doubt that a fourth dose will be necessary, but the exact timing of this dose has not yet been decided. This reinforcing dose is expected to establish long-lasting immunity in those already possessing basic immunity and to increase the over-all protection rate above the 90 per cent. obtained. But poliomyelitis vaccine, like all other vaccines and toxoids, does not protect everyone, as a few persons apparently cannot respond normally to the antigens.

The degree of cross-protection (if any) between the three types of poliomyelitis virus in man has not yet been assessed; laboratory investigations indicate that the types are sharply defined with little overlap of protection between them.

Effect of immunization on the carrier rate.—Formolized vaccine reduces considerably the incidence of paralytic poliomyelitis, and there is also some suggestion of reduced pharyngeal carriage. It does not, however, prevent alimentary infection or influence the quantity of virus in the stools and the duration of excretion. This finding may have to be revised when highly potent vaccines have been tested. It may well be that widespread, efficient vaccination may reduce the reservoir of carriers in the community. As inactivated viruses cannot multiply, formolized vaccine cannot *cause* a person to become a carrier.

WHO SHOULD BE VACCINATED AND WHEN?

The Ministry of Health has recommended the following priority groups for vaccination:—(1) persons between the ages of 6 months and 25 years, (2) expectant mothers, (3) general practitioners, a wide range of hospital staff (all those who come in contact with patients), medical students, ambulance drivers, and families of these groups. In addition to the Ministry's priority groups, the position of adults going abroad—for example, in the Services—and parents with children of school age, should be specially borne in mind. In some countries, persons up to 40 years of age are vaccinated. There is, in fact, no upper age limit for poliomyelitis vaccination: some severe paralytic cases have occurred recently in Great Britain above the age of 60 years.

The youngest age at which vaccination against poliomyelitis can be practised is still under investigation. Many new-born infants in this country possess high levels of placentally transmitted antibodies to all three types of poliovirus in their blood, especially if, as a result of the immunization policy, the mother was vaccinated against poliomyelitis during pregnancy. Maternal antibodies appear to interfere with the infant's response to the vaccine; in most cases these have disappeared by six months. Seven months is the earliest age at which uniformly good response to active immunization can be expected with present-day vaccines. The immunization of pregnant women as recommended by the Ministry not only protects a group of per-

sons particularly susceptible to attack but also confers on babies a passive immunity of sufficient duration to enable immunization with combined antigens (diphtheria-tetanus-pertussis) to be carried out between the second and sixth months without incurring the slight risk of development of provocation poliomyelitis.

The relationship of vaccination against poliomyelitis to other immunizing procedures.—It is a sound principle to separate smallpox, yellow fever and BCG vaccinations from poliomyelitis vaccination by an interval of three or four weeks, although in exceptional circumstances poliomyelitis and one of the other inoculations have been performed at the same session. In the presence of a smallpox epidemic, vaccination against smallpox should, of course, have priority. Much interest has been aroused in the possibility of using a quadruple (diphtheria-tetanus-pertussis-polio) vaccine. The results so far obtained in Canada and the United States are very encouraging. Further research is needed, however, on the preparation of balanced mixtures and on the effects of immunological interference from the transmission of trans-placental antibodies. It is highly probable that a quadruple prophylactic will eventually be widely adopted in this country.

LIVE VACCINE

Since the Salk-type vaccines in current use have not given strong and *lasting* immunity without a three-dose course, followed by reinforcement with a fourth dose, the search for more effective poliomyelitis vaccines has naturally received considerable attention. Three American workers, Sabin, Koprowski and Cox, have independently prepared live vaccines from specially selected, attenuated strains, which are administered orally and are cheaper to produce than formolized vaccines. The viruses multiply in the alimentary tract, and, like naturally occurring strains, are excreted in the fæces and can spread from person to person. So far there has been no evidence that live attenuated vaccine has produced a more durable immunity than inactivated vaccine. Moreover, a serious drawback has emerged: certain strains, recovered from the fæces, have shown an increase in virulence, as demonstrated by illness, with paralysis, in monkeys. This has indicated that the attenuation of the cultures has not been stabilized.

Research continues to obtain a safe 'live' vaccine which might at least be used to reinforce the Salk-type vaccine. There is also a possibility that this procedure might replace and eliminate wild polioviruses from a well-vaccinated community. Perhaps the most acceptable application of these strains may be in face of an epidemic. Feeding of an attenuated strain to a high proportion of the population might result in the displacement of the virulent strain in circulation through a community and a halting of the epidemic. The interfering action of attenuated virus may be more useful than its ability to produce basic immunity, which has been disappointingly low in some of the strains already tried.

I wish to thank my colleague, Dr. A. P. Goffe, for a number of valuable suggestions.

COMBINED PROPHYLAXIS

By WILFRID GAISFORD, M.D., M.Sc., F.R.C.P.
Professor of Child Health and Pædiatrics, University of Manchester

In any schedule of immunization combined prophylaxis is essential, because only by its use can an adequate number of infants in the community be protected. It is advisable to limit the number of injections if parental cooperation is to be achieved and if active resentment on the part of the recipient is not to lead to psychological disturbance.

THE FIRST MONTH

One of the most important problems is to determine the earliest age at which immunization can satisfactorily be begun. Clearly, if it were feasible, the new-born period would be best, because of the ease of access to the infant and the greatest chance of full maternal cooperation and because the earlier immunization is started the sooner will it be completed and the greater will be the period of protection in the vital first year of life when infections such as pertussis and tuberculosis are most fatal.

There is considerable difference of opinion as to whether infants in the first month of life can respond adequately to active antigenic stimulation. There are two possible hindrances to successful response: (1) the existence of so-called 'immunological immaturity', and (2) the inhibition of active antibody formation by placentally transmitted antibody, which is known to occur in relation to diphtheria, poliomyelitis and other infections if the mother has high titres of these, either as the result of previous infection or after her own immunization. With regard to the first it is true that the response is not as good in the new-born period but, with increased antigenic stimulus (either from improvements in, or increased dosage of, the material used, or by incorporating an adjuvant such as aluminium phosphate or hydroxide), antibody levels usually considered in the protective range may be achieved. In other words, if the prophylactic agent used is sufficiently potent the infant will respond. Failure of response is more probably due to a weak antigen or to insufficient dosage than to any inherent defect in the infant. With regard to the inhibition of active response caused by passively transferred antibody, this, too, may possibly be overcome by increasing the antigenicity or the dose of the vaccine or other agent used and there is evidence that, as regards diphtheria at least, *sensitivity* is achieved if alum is used as an adjunct and that a satisfactory response to a booster dose later will be obtained. As these agents go on getting progressively better it may well come about that primary immunization will be begun in the new-born period as a routine.

If, however, there is some dispute about immunization in the new-born period, there is no disagreement with the general principle that it should be started as early as possible. Besides reducing the number of injections, combined prophylactics may well be mutually enhancing and, although this enhancement is hardly likely to be so great that the primary course can be reduced to two injections instead of the customary three, the degree of protection afforded will be higher. For any such effect to result, however, it is of great importance that the proportions of the various constituents

should be correctly balanced; otherwise the opposite effect may follow and the response of one or more of the antigens may be suppressed.

THE CHOICE

Prophylactics may be 'combined' by formula, or by being mixed immediately before injection, or separate antigens drawn up into the same syringe, or the combination may be achieved by giving more than one antigen at the same time but in different sites: for example, BCG may be given into the arm and a triple antigen into the buttock. There are many possible combinations: for example, diphtheria and pertussis (D.P.), diphtheria and tetanus (D.T.), pertussis and tetanus (P.T.), diphtheria, pertussis and tetanus (D.P.T.), and typhoid, paratyphoid A and B and tetanus (T.A.B.T.) being already well tried. There will doubtless be further extensions and the most likely one in the immediate future is a quadruple antigen incorporating poliomyelitis with D.P.T. Such a preparation is, indeed, already in use in Canada and the United States. Of the available combinations for primary immunization in infancy the generally recommended ones are D.P. and D.P.T.

It may be argued that, as tetanus is most unlikely in infancy, immunization is unnecessary until later and that, as diphtheria is no longer a menace in infancy, the time factor is of less importance than the fact that all children should be immunized at some time before they go to school. This would leave pertussis vaccine as the sole remaining urgency in infancy and would suggest that diphtheria and tetanus toxoids might be combined and given later. As, however, balanced triple antigens are readily available it is more practical to give these as the primary course and continue with booster doses as required, using the same combination. Exposure to a particular infection later would, of course, call for an immediate injection of the specific antigen concerned. This last point raises a matter of some importance. Triple antigen is available in two forms: a simple suspension and one containing an adjuvant, usually either aluminium phosphate or aluminium hydroxide. Most of the available evidence points to the superiority of the alum vaccines for primary immunization in infancy—and indeed for booster doses—but, on exposure to a particular infection—for example, tetanus—when a rapid response is urgently needed, a fluid toxoid should be used. The same holds good when a booster dose of pertussis vaccine is given after contact—as it should be if the exposure occurs six months or more after immunization. In each case the dose need not exceed 0.25 ml.

The enhanced value of alum-containing antigens should not be overlooked, even though they have fallen into disrepute on account of the risk that they may provoke paralytic poliomyelitis, for this is an extremely unlikely complication in early infancy: that is, under the age of six months. The risk, as is well known, also extends to mixed antigens without alum, so that if this provocative effect is allowed to dominate the picture we should be forced to use single plain antigens and the result would certainly be a

marked reduction in the number of infants in the community who were adequately protected. Giving poliomyelitis vaccine as the first immunization, in order that the protection afforded thereby might allow of the subsequent combined prophylaxis without the risk of provoked paralysis, is unfortunately impracticable because adequate response to the current poliomyelitis vaccines cannot be regularly achieved with certainty until infants are about eight months old—by which time they ought rightly to have almost completed their combined prophylactic primary immunization. The value of pertussis immunization would certainly be reduced by more than half if it were so long delayed.

OVERCOMING THE POLIOMYELITIS RISK

There are two possible solutions in overcoming the poliomyelitis risk. The first is the preparation of a more antigenic poliomyelitis vaccine, particularly in regard to the Type I component, which will be effective in the first month of life and which will combine with triple antigen without adversely affecting the response of any of the components. The second is the antenatal immunization of the mother with poliomyelitis vaccine, thereby endowing the infant with such high titres that he may be protected during the first few months of life and may be successfully immunized with alum-containing triple antigen during this time and then be actively immunized against poliomyelitis during the second half of the first year. If the mother is given pertussis vaccine antenatally to protect the infant against pertussis in the first months of life, as has been suggested from time to time, there is one great drawback: the period during which maternal protection has waned to non-protective levels and active immunization has not yet been achieved. This would be from the age of about 3 months to 6 to 8 months, and during this time the infant would be at risk and dependent solely on his non-specific immune powers, together with therapy, if he acquired infection. In other words, the risks of giving this prophylaxis antenatally are too great to make it a really profitable solution.

With regard to poliomyelitis alone, however, there may be more value, and antenatal immunization could easily become a routine procedure, just as has blood testing. If this were done, and alum-containing D.P.T. were given at 1, 2 and 3 months, active poliomyelitis immunization could follow at 9, 10 and 11 months. This would provide the earliest possible protection against pertussis but might produce an inadequate response to the diphtheria component because of the inhibitory effect of maternally transmitted antitoxin and despite the undoubted enhancement of the diphtheria response from the pertussis component as well as from the adjuvant. It is also of importance that the initial antigenic stimulus should be as powerful as possible because this has a direct relationship to the final response. Results in a recent investigation have shown that the diphtheria response to this schedule is excellent when the maternal antitoxin titres are low, but that the expected interference occurs when high titres are present. It is hoped that

the findings after the next dose at 18 months will show that the primary course succeeded in sensitizing the infants and that a good booster response has followed. The tetanus antitoxin levels and, most important of all, the pertussis agglutinin titres, are also most satisfactory and the levels of poliomyelitis neutralizing antibody titres are certainly far in excess of those considered protective.

The combined poliomyelitis-D.P.T. antigen presents certain disadvantages, for it cannot be given to protect with certainty against poliomyelitis or diphtheria until after six months of age, by which time, as stressed earlier, its pertussis-protection value will already have been greatly lessened. With improved antigenicity of the Type I component of the poliomyelitis vaccine, however, this may well become the accepted prophylactic of the future.

Finally, in considering combined prophylaxis, protection against tuberculosis should not be overlooked. In infancy, which is the optimal time for ensuring protection against tuberculosis, BCG vaccine should always be injected into the arm. Provided the arm in which BCG is injected is kept free from other injections for six months there is no contraindication to the simultaneous administration of other antigens. As most injections in infancy are best given into the buttock no difficulty should be experienced in combining BCG whenever desired.

AN IMMUNIZATION SCHEDULE

To ensure reasonable protection it is recommended that a schedule which might be adopted at present is as follows:—

(i) At the end of the first month of life:	First injection of 1 ml. of alum-containing triple antigen. (BCG simultaneously if desired.)
(ii) At 2 months.. ..	2nd injection, 1 ml. of alum-containing triple antigen.
(iii) At 3 months.. ..	3rd injection, 1 ml. of alum-containing triple antigen.
(iv) At 9 months.. ..	1st injection of poliomyelitis vaccine, 1 ml.
(v) At 10 months ..	2nd injection of poliomyelitis vaccine, 1 ml.
(vi) At 11 months ..	3rd injection of polioymelitis vaccine, 1 ml.

The third poliomyelitis injection is recommended because of the markedly improved response which has been found as compared with that following two injections in this age-group.

An efficient well-balanced combined poliomyelitis-D.P.T. prophylactic at 18 months of age would finish the programme until the age of school entry when a D.T. booster should be given, probably together with poliomyelitis when this combination becomes available. There is no need to repeat the pertussis vaccine after 18 months of age, but it remains a valuable emergency prophylactic to be given immediately after any known contact during the pre-school years.

THE USE OF GAMMA-GLOBULIN

By THOMAS ANDERSON, M.D., F.R.C.P.Ed., F.R.F.P.S.
Professor of Infectious Diseases, University of Glasgow

GAMMA-GLOBULIN is the serum component which contains the bulk of the measurable circulating antibodies although it seems that smaller amounts may be present in the beta-globulin fractions. So far as the individual is concerned, therefore, a sample of his gamma-globulin may be expected to portray his past experience of antigenic stimuli whether sustained naturally or artificially. It will represent a concentrated essence, as it were, of what we might expect to find from a close immunological study of his whole serum. The extent of this concentration will depend upon the particular process used but it may be assumed that 1 ml. of the gamma-globulin fraction will contain the antibodies which would have been found in some 10 to 20 ml. of the person's whole serum. In this country the material is often supplied in freeze-dried form and reconstituted with distilled water before use. Although it may seem too simple to be worth expression it needs to be said that the gamma-globulin will contain nothing which was not already present in the original plasma or serum.

TYPES OF GAMMA-GLOBULIN

When the serum from a number of donors is pooled and gamma-globulin is prepared from that material, the antibody content will be a reflection of the common infections of the community in which the individuals live. When an infection is commonplace, the antibody content may be expected to be high; when a specific infection is uncommon the content may be small or indeed absent. Pooled adult serum gamma-globulin therefore is not a 'standard' material but is likely to vary in its content of different antibodies from country to country and, indeed, perhaps between different classes of the same country.

In order to reduce the vagaries of ordinary adult gamma-globulin two devices may be used. First, advantage may be taken of the natural occurrence of a particular infection in the adult to secure a supply of convalescent serum which at this period may be assumed to be rich in specific antibody. When this is transformed into gamma-globulin it can be expected to contain these antibodies in high concentration. Such serum might have added immunizing effect against the specific infection involved (e.g. convalescent measles serum gamma-globulin). Second, advantage may be taken of a known and effective method of active immunization to induce in a donor a high concentration of serum antibodies which would thus produce a globulin of enhanced potency (e.g. post-smallpox-vaccination serum gamma-globulin).

Each of these gamma-globulins is, of course, different from the others.

Pooled adult serum gamma-globulin may be expected to contain a reasonable range of antibodies, the highest concentration being against those infections which the majority of the individuals have encountered. *Convalescent serum gamma-globulin* will be particularly rich in all the specific antibodies which have resulted from experience of and recovery from the infection concerned. *Post-vaccination gamma-globulin* will be potent in regard to the antibodies induced by the vaccination process, although it may well be that the artificial antigenic stimulus may not always result in the production of all types of protective antibody.

MODE OF ACTION

When globulin is injected intramuscularly the individual receives a form of passive immunization. By analogy with horse serum containing diphtheria or tetanus antitoxin therefore such material might be used in prevention or in treatment, with perhaps the advantage that since the gamma-globulin is of human origin the risk of sensitization reaction would be reduced. It is, however, reasonable to infer that the protection conferred will be maximal shortly after the injection and that thereafter there will be a steady loss of antibody until, at the end of three to five weeks, the individual reverts to his original susceptible state. It was thus natural to speculate that there was a useful place for gamma-globulin in the prevention of certain infections, in particular of those for which no other method of specific prevention was available.

In so far as its application to the treatment of an infection is concerned, the subject must become perhaps more speculative. It may be that the introduction to the patient's blood of a small addition of gamma-globulin can confer some benefit quite apart from its content of antibody. When used in this way, however, it would seem possible that rather large doses might be necessary if benefit were to result. When the object of the therapeutic exercise is to supply the patient with ready-made antibody, again we must consider certain difficulties. Bacterial infections are now so effectively brought under control by chemicals or antibiotics that there is seldom a need to consider the use of immune serum—human or animal. As a result, the application of gamma-globulin in treatment is usually confined to conditions presumed or known to be caused by viruses, and it must at once be said that in many of these we are still lamentably ignorant of the precise way in which the virus acts. In some there is reason to believe that virus is present in the blood at the onset of symptoms so that the introduction of antibody at such a stage might well prove ameliorative. But in many others it would seem possible that viræmia—if it occurs—precedes the presentation of those signs and symptoms which are diagnostic. By the time a diagnosis can be established in such circumstances the virus may well have reached an intracellular station and the presence of specific humoral antibody might have little or no beneficial effect.

Some of these considerations may seem to be largely theoretical and must not be assumed to deny categorically the possibility of the demonstration of some effect. They should, however, induce a proper scepticism regarding reports of beneficial action in single or small groups of cases and, in view of the well-known variability in human response to infection, they should suggest the absolute need for properly controlled experiments.

CRITERIA FOR THE USE OF GAMMA-GLOBULIN AS A PROPHYLACTIC

Under the carefully controlled conditions of a laboratory experiment it is easy to demonstrate the preventive effect of antibody administration. In practice all kinds of complicating factors are present. It may be noted that the only applications of the principles of passive immunization which have stood the test of time are the administration of tetanus antitoxin to the wounded person at the time of injury, and the administration of convalescent serum to the contact of measles. It may be that these two examples will allow the formulation of certain useful general principles.

(1) The infection to be prevented should be one which will usually be brought to medical notice and in which a confident and correct diagnosis will be possible. If the diagnosis of the primary case producing the contact is to depend solely upon the patient's statement (as so often in rubella, for example) then grave doubts must arise when the method succeeds or even if it fails.

(2) The precise time of contact must be known. It would seem at least possible that a stage in incubation of the infection can be reached when the comparatively small amount of globulin injected would prove incapable of coping with the massive production of virus.

(3) For the same reason the incubation period should neither be too short nor too long. When it is very short it may give insufficient time for effective action; when it is too long it may permit the individual to lose his passive immunity before general release of the virus occurs.

(4) Exposure should normally result in the infection of the susceptible person with the production of the florid disease. For certain infectious diseases this means that the usual method of spread of the disease would be from case to case. When the diagnosable case of infection is but one of many unknown and undiagnosable infections, the person who has received gamma-globulin may continue to be exposed after the period of passive immunization has lapsed. In the case of the poliovirus, where many persons are infected but few develop paralysis and where the passively immunized person may indeed show enteral infection, globulin would not seem to be the natural choice of prophylactic for field use. In rubella, too, exposure does not always result in infection so that apparently successful results from individual attempts at passive immunization may be misleading.

(5) The circumstances should not be continually recurring. It would seem—on general grounds quite apart from the possibility of inducing sensitization—undesirable to suggest that the state of passive immunization should be produced continuously or at frequently occurring intervals by a system of repeated injections. One obvious exception to this general consideration would be the management of the proven case of hypo-gamma-globulinæmia in which, of course, special circumstances arise.

(6) The method of passive immunization should be regarded as a form of personal protection not applicable widely to the community. This does not exclude its possible efficacy in a small, circumscribed or closed community (such as a children's

ward) in which it is precisely known that all of the occupants experienced exposure at exactly the same time. In the open community exposure is liable to vary in time and in amount. In such circumstances a general use of globulin may produce very variable results. Quite apart from this, the use of gamma-globulin on a wide scale raises questions of expense and general availability of the material. The stage could almost be reached where one half of the community was receiving, in effect, a small blood transfusion from the other half—a not very useful expenditure of time and energy.

GAMMA-GLOBULIN IN PROPHYLAXIS

Measles.—The basis for the use of adult serum gamma-globulin in the prevention of measles is sound and is attested on much personal experience of many doctors as well as having the authority of adequately controlled field experiment. Gamma-globulin is also a safe substance and the danger of homologous serum jaundice—a rare but undoubted hazard of pooled convalescent measles serum—would seem to be eliminated. In considering its use, however, we must bear in mind the fact that the antibiotics have made measles a much less serious infection than it was twenty years ago. The College of General Practitioners indeed has shown that in many children the infection requires no specific treatment at all. Gamma-globulin therefore should be used only in eliminating measles as a cross-infection of children's wards, and in preventing the disease in weakly children under the age of eighteen months. In children's wards it needs to be emphasized that it is only of value when given at once to all children (irrespective of a history of previous attack) on their primary ward exposure. When two or three cases occur more or less simultaneously a missed primary case can be inferred and in such examples gamma-globulin often seems to be ineffective. Even when prevention is not actually secured the effect of gamma-globulin may be to alleviate the infection so greatly that the child suffers little upset. When prevention is the aim the dose for a child under 2 years should be 500 mg. Attenuation may be secured with half of this dose.

Rubella.—Recent correspondence in the medical press shows very clearly the divergence of opinion on the action to be taken when rubella occurs in the early months of pregnancy. It would be nice to be able to be dogmatic regarding the efficiency of gamma-globulin as a prophylactic. Unfortunately there have been few controlled experiments, and the results have sometimes been contradictory. An explanation of this may well lie in the variation in the content of rubella antibody between different lots of globulin. (Presumably the very fact that rubella is often encountered in adults indicates that there is a low infectivity rate during childhood in the ordinary community). It seems possible therefore that one reason for failure is the use of too small a dose and it has been suggested that to secure prevention a dose of 1,500 to 2000 mg. is required. This, of course, will mean that an amount of the order of 20 to 25 ml. will need to be injected. When the circumstances of contact are known with precision, the primary case accurately diagnosed, and the contact a known susceptible very early in

pregnancy, the use of convalescent serum gamma-globulin may be considered. This material is scarce and should not be wasted.

Poliomyelitis.—Now that there is an effective method of active immunization with poliovirus vaccine, gamma-globulin should be regarded as having no practical application in the prophylaxis of poliomyelitis in the normal community.

Infectious hepatitis.—Naturally occurring infectious hepatitis can be prevented by the injection of an adequate amount of gamma-globulin. For an adult this will mean a dose of 1,500 mg. In this infection, however, there are many subminimal attacks so that in general practice the apparent success of the immunization may be illusory. It has, however, proved very effective in curtailing an epidemic among the adult staff of an institution in which the children seemed to be a constant source of infection. Gamma-globulin does not prevent homologous serum hepatitis.

Both in poliomyelitis and in infectious hepatitis it seems possible that the administration of gamma-globulin may permit a form of active-passive immunization. If exposure to the virus is continuous throughout the period of passive immunity, infection may be acquired under the diminishing protection of the gamma-globulin so that the individual is encouraged to produce his own neutralizing antibodies. Although such reasoning should encourage the consideration of a place for gamma-globulin as a temporary measure in small circumscribed communities it does not invalidate the general argument that in the normal type of community the method has little to commend it.

Smallpox.—Antivaccinal gamma-globulin (prepared from the serum of recently vaccinated or revaccinated adults) is available. It may be injected at the same time as, or twenty-four hours after, the performance of vaccination on contacts. It would seem especially desirable to take this added precaution with individuals who have never been primarily vaccinated and who become close contacts of a case of smallpox. Dosage should be of the order of 1,500 to 2000 mg. for an adult. It is sometimes essential to vaccinate an individual who suffers from a severe form of eczema. The use of gamma-globulin in such persons would seem to be a prudent measure in order to minimize the risk of systemic dissemination of the vaccine virus.

Chickenpox, whooping-cough, mumps.—There is no convincing evidence that gamma-globulin in reasonable dosage can play any useful part in the prevention of these diseases.

GAMMA-GLOBULIN IN THERAPEUTICS

It has already been indicated that gamma-globulin has not a very important place in therapy. The diagnosis of *hypogammaglobulinæmia* has been made with greater frequency in recent years. In some of these cases the condition seems to have the characteristics of an inherited defect. Pooled adult gamma-globulin has been given monthly to such children and it may be that for this

type of case such therapy will require to be prolonged indefinitely. In other cases the defect is observed in the course of an infection and appears to be temporary. Such persons may benefit from the administration of gamma-globulin on one or two occasions.

In some cases of *generalized vaccinia* and *Kaposi's varicelliform eruption*, recovery has seemed to date from the administration of gamma-globulin. In certain forms of *encephalitis* (e.g. after smallpox vaccination or measles) the administration of post-vaccination or convalescent gamma-globulin has been advised. The reports of its efficacy have not been completely convincing. Nonetheless, the entire absence of any other method of treatment may force the clinician to consider any measure which might prove beneficial. As controlled experiments in man would be difficult to plan one must look to the laboratory to produce worth-while evidence on this controversial subject.

CONCLUSION

Gamma-globulin is an interesting and useful by-product of the blood transfusion service. It is moderately expensive and, if for no other reason, this should encourage thoughtfulness in its general application.

Its effectiveness in measles and smallpox prevention rests on sound evidence.

Its practical value in the prevention of rubella is not conclusively proven. In the case of close contact with a definite case of rubella the use of gamma-globulin in high dosage is suggested.

It is argued that in the open community gamma-globulin has little practical place in the prevention of poliomyelitis or infectious hepatitis.

The importance of gamma-globulin to the body's economy is not yet fully understood. Why does the hypo- or agamma-globulinæmic child manage to survive so long despite the assault of bacterial and virus infections? It would appear that a better appraisal of the place of gamma-globulin in therapy must await a deeper knowledge of all the ways in which man keeps his infections in check.

THE PRESENT STATUS OF BCG

By K. NEVILLE IRVINE, D.M.

Medical Director, BCG Control Centre

THE first report of the Medical Research Council's trial (1956) has changed the status of BCG in this country from a controversial innovation to an accepted prophylactic procedure; the trial not only showed that BCG was effective but measured the amount of protection it gave. Among the non-reactors who were vaccinated the incidence of tuberculosis was 0.37 per thousand, whilst the rate for unvaccinated non-reactors was 1.94; in other words BCG protected four out of five. These findings are generally regarded as conclusive, although some still dispute them in the United States.

BCG is a live vaccine made from a bovine strain of the tubercle bacillus which was rendered avirulent forty years ago by Calmette and Guérin (Bacille Calmette-Guérin). Until recently only Danish fresh BCG was available in this country. As this was imported by the Ministry of Health and issued only to approved vaccinators for use only on persons exposed to tuberculosis or thirteen-year-old school children, the position of the general practitioner was that of a spectator. Now that freeze-dried BCG is manufactured in this country the vaccine may be bought and used by any doctor: the general practitioner need no longer remain a passive onlooker.

Immunization against several of the endemic diseases of this country is already carried out by the general practitioner. Should he not add BCG vaccination to his list? The answer is that some special knowledge and skill are required for this form of immunization, lacking which a doctor would be well advised to leave it alone. He must be able to give an intracutaneous injection, carry out and read a tuberculin test, and understand clearly the underlying theory. This is admittedly new ground for the older practitioner, but it is surprising that young doctors are still leaving hospital without having done an intracutaneous injection or read a tuberculin test. Descriptions of these techniques are given elsewhere (Irvine, 1957), but they are best learnt by a short course of practical instruction under a competent vaccinator.

THE THEORY OF BCG VACCINATION

The theory of BCG vaccination is given most succinctly as six aphorisms.

(1) *A person who has not been infected with tubercle bacilli has no allergy to tuberculo-protein.* If tuberculo-protein in the form of tuberculin is used as a skin test on an uninfected person, no reaction occurs; the tuberculin test is negative.

(2) *The first or 'primary' infection evokes resistance to the tubercle bacillus and allergy to tuberculin.* This occurs three to six weeks after infection. Whether allergy is part of this acquired resistance or not is still a hotly

debated point. In certain circumstances the infection may overcome this acquired resistance and progressive tuberculosis results; usually the resistance is adequate to check the invading organisms and imprison them in fibrous tissue while the lesion is still so small that it cannot be detected clinically or radiologically. The only indication that such a subclinical infection has taken place is the appearance of allergy to tuberculo-protein; the tuberculin test becomes positive.

(3) *Subsequent infections are immediately opposed by acquired resistance.* Most subsequent infections are speedily annihilated, although in certain circumstances progressive tuberculosis may occur despite the presence of acquired resistance. Thus, a subclinical primary infection acts as a vaccination against subsequent tuberculous infections.

(4) *BCG vaccination produces a harmless primary infection of the skin.* Because BCG is a live tubercle bacillus, vaccination with BCG produces a primary focus. Because BCG is non-pathogenic, this primary focus is benign and progressive tuberculosis does not result.

(5) *BCG vaccination evokes resistance to the tubercle bacillus and allergy to tuberculin.* This usually occurs three to six weeks after vaccination but, as BCG is an avirulent strain, it may take longer. As there is as yet no test for acquired resistance, the appearance of allergy has to be accepted instead. A positive post-vaccination tuberculin test indicates successful vaccination.

(6) *The vaccination of a tuberculin-positive person is unnecessary and undesirable.* The presence of allergy shows that infection has taken place; this may be due to a virulent infection or to BCG. In either case acquired resistance has already been evoked, so no further good can be done by vaccinating. Because of the presence of acquired resistance, the local reaction to vaccination is likely to be both rapid and fierce (Koch's reaction), which is undesirable. It follows therefore that all persons other than new-born infants should be given a prevaccination tuberculin test to exclude a previous subclinical infection and only non-reactors should be vaccinated.

THE TUBERCULIN TEST

There are two forms of tuberculo-protein used in this test: Old Tuberculin (OT) and its Purified Protein Derivative (PPD). In most cases it is immaterial which is used as the results are similar and both are measured in tuberculin units (TU). To test for allergy to tuberculo-protein, OT or PPD can be brought into contact with the skin by a variety of methods; only two are used in conjunction with BCG vaccination in this country: the Mantoux test and the Heaf multiple-puncture test.

The Mantoux is the standard against which all others are assessed. The test is performed by injecting 0.1 ml. of a dilution of OT or PPD intracutaneously with a tuberculin syringe. To inject this small dose of fluid accurately between the dermis and epidermis of a struggling child requires skill.

The Heaf multiple-puncture test is given by stabbing six needles through a film of special glycerinated PPD spread on the skin. This is done with the

Heaf multiple-puncture apparatus, more familiarly known as the Heaf gun, which has six needles drawn up behind an end-plate perforated with six corresponding holes. The end-plate is placed on the skin over the film of tuberculin and the gun fired; the needles stab through the holes in the end-plate to a depth of 2 mm. In the latest model (made by H. G. East & Co. of Oxford) the gun fires itself when the end-plate is pressed on the skin with the correct degree of firmness. The great advantage of the Heaf test is that it requires no skill to perform. It causes little pain and is much preferred by children to 'the needle'. When read at seven days its results are comparable with those of the Mantoux 100 TU (British Tuberculosis Association, 1959). As a result it is rapidly becoming the tuberculin test of choice in this country.

VACCINATION

Non-reactors to the prevaccination tuberculin test should be vaccinated forthwith. BCG vaccine is supplied either as a fresh suspension (Danish) which must be used within two weeks of manufacture, or as a dried solid (British) which has a life of twelve months; both vaccines must be protected from sunlight and heat. The dried vaccine is reconstituted by the addition of 1 ml. of sterile water; once an ampoule of either vaccine has been opened it should be discarded at the end of the vaccination session.

BCG may be inoculated into the skin in different ways, but in this country the intracutaneous method only has been used up to the present; trials of a multiple-puncture method are now in progress in an attempt to simplify the technique of vaccination. A dose of 0.1 ml. of the vaccine (0.05 ml. for infants under 12 months) is injected intracutaneously over the insertion of the deltoid, over the angle of the scapula, or into the antero-lateral surface of the thigh; this last site should be avoided in infants.

The local reaction to intracutaneous vaccination roughly resembles that of smallpox vaccination, but its evolution is slower. About two weeks after vaccination a painless papule appears which increases in size up to six weeks when it may measure 20 mm. in diameter; over half these papules break down to an ulcer up to 10 mm. in diameter which may persist for as long as three months. The papule takes about a year to disappear, usually leaving a small scar. A slower reaction takes place in the regional lymph nodes, which generally runs a silent course though some painless enlargement may be found. It is not uncommon to find calcification in these lymph nodes as early as a year after vaccination.

Conversion testing and follow-up.—A second tuberculin test may be carried out six weeks or more after vaccination to prove that the vaccination has 'taken'. This test should be positive. The change from a negative prevaccination test to a positive postvaccination test is called 'conversion'. Follow-up tests may be carried out yearly; as long as they are positive the vaccination is regarded as still effective, which is usually for a period of at least five years. If the follow-up test eventually changes back to negative, this is known as 'reversion' and the person should be revaccinated.

VACCINATION OF CONTACTS

The vaccination of those whose work or home life brings them into contact with open tuberculosis is complicated. As a negative tuberculin test only means that the person was not infected up to three to six weeks previously, contacts should be segregated from known infectious tuberculosis for six weeks before prevaccination testing. Moreover, as the vaccination cannot be considered effective until conversion has occurred, a total period of segregation of some twelve weeks may be required. In practice this may be difficult; if it is impossible it is better to vaccinate contacts without segregation than not to vaccinate them at all. There is no evidence that vaccinating in the pre-allergic phase of a natural infection is in any way harmful, although the evolution of the local vaccination reaction may be more rapid: an 'accelerated reaction'. All tuberculin-negative contacts should be vaccinated regardless of age.

VACCINATION OF NON-CONTACTS

The vaccination of those who are not in contact with tuberculosis is simple. A prevaccination test (which may be omitted in new-born infants) is followed immediately by vaccination and six weeks later by a postvaccination conversion test. In school children the conversion rate has been found to be so consistently high that postvaccination testing is now generally omitted; the conversion rate and local reaction of each batch of British vaccine are checked in any case by the BCG Control Centre. Recent work suggests that a vaccination that shows any local reaction may be regarded as successful (Irvine and Barr, 1959). The optimum age for the vaccination of non-contacts in this country is 10 to 15 years.

COMPLICATIONS AND THEIR TREATMENT

As Parish (1958) points out, there have been fewer fatalities reported from BCG than from any other inoculation; only four deaths have been recorded in over 150 million vaccinations. Most complications of vaccination are an exaggeration of one of the usual reactions to a degree which renders it unpopular to the lay public. Such complications are papules over 20 mm., ulcers over 10 mm., and indolent lesions that take more than three months to heal. The last two should be dressed twice a day with an ointment such as 'hydroderm' (Riches, 1958) which will promote rapid healing in most cases. A cold abscess the size of a cherry may occur at the site of vaccination if the vaccine has accidentally been given subcutaneously; a single aspiration of the pus is all that is needed.

The most troublesome complication is a cold abscess of the regional lymph nodes; this occurs most commonly in infants and is uncommon over the age of five. Halving the dose for infants has reduced the incidence without materially affecting the conversion rate (Gaisford and Griffiths, 1954). Treatment is by aspiration and replacement of the pus by 10 to 20 mg. of streptomycin; this may have to be repeated more than once. Simple incision is strongly contraindicated as the wound may take months to heal.

In addition to these, one case of lupus at the site of vaccination has been reported in this country and a few more from abroad; this rare condition responds readily to antibiotics.

PRACTICAL POINTS

Don't promise immunity from tuberculosis: BCG vaccination only protects four out of five.

The fact that an infant has been vaccinated should be recorded prominently on his medical record card and should be mentioned in any letter to a hospital; otherwise the discovery of a positive tuberculin reaction may lead to an erroneous diagnosis of tuberculosis.

Little is known of the interaction of BCG with other inoculations. The Ministry of Health advises that BCG should not be given for four weeks after inoculation against yellow fever, poliomyelitis or smallpox; it would seem prudent to leave any inoculation after BCG vaccination until the local reaction is settling. Abscess of the regional lymph nodes may be provoked by inoculations into the same limb within six months of BCG vaccination; for this reason it is better to vaccinate the right arm with BCG, leaving the traditional left arm free for other inoculations.

The only contraindication to BCG vaccination is a positive tuberculin reaction.

In moments of anxiety remember that, with the single exception of lupus, all complications always ultimately heal—even if wrongly treated.

SUMMARY

The release of a British freeze-dried BCG vaccine on the open market makes it essential that every practitioner should be conversant with the theory of tuberculin testing and vaccination, if not with the practice.

Although the Mantoux has in the past been the standard tuberculin test, the Heaf multiple-puncture test is becoming increasingly popular because of its simplicity.

BCG vaccination is safe and protects four out of five of those vaccinated. Nearly all complications ultimately resolve themselves without treatment, but measures are described which expedite this resolution.

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INFLUENZA IMMUNIZATION

By ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.
Professor of Bacteriology, University of Edinburgh

INFLUENZA in its typical clinical form is a short, sharp febrile illness of two to four days' duration associated with respiratory symptoms, headache, prostration and some generalized aching. The term 'influenza', however, is used by both doctor and layman for various kinds of respiratory infection due to a variety of known and unknown etiological agents, among which are included the influenza viruses. Since the discovery of influenza virus A in 1933 and influenza virus B in 1940 over thirty respiratory viruses have been identified, some of them associated with clinical syndromes such as pharyngitis, croup and atypical pneumonia, and others with the febrile catarrh or acute respiratory disease (ARD) which can closely simulate influenza. Even so, it is pretty certain that the etiology of many febrile catarrhs is still to seek and that these illnesses are often labelled 'influenza'. When epidemic waves of influenza occur, however, and the clinical syndrome is supported by laboratory evidence of specific virus etiology, the picture becomes less blurred and it is in such circumstances that the protective value of influenza virus vaccines may be assessed.

Epidemics of influenza due to virus A occur in this country at two- to four-year intervals and outbreaks of virus B influenza in less frequent cycles. Thus, in recent years with increased laboratory facilities for accurate diagnosis, virus A influenza was shown to be the prevalent infection in 1949, 1951, 1953 and 1956, whilst virus B influenza was epidemic in 1946, 1950, 1954 and, along with A, in 1958-59. At much longer intervals, pandemics of influenza occur, as in 1889, 1918 and 1957. Although only the last of these pandemics was proven to be due to a new variant of influenza virus A, it seems likely from serological and other evidence that the earlier outbreaks were also due to this virus.

When influenza occurs in epidemic form in a community, there is a sudden marked increase in sickness absenteeism in schools and industry and the general practitioner's list of visits quickly reaches almost unmanageable size. This is followed by a greatly increased demand for hospital beds and a rise in the death rates among elderly people. Thus, a dislocation of education and industrial effort and a very heavy strain on the medical and nursing professions occurs with remarkable frequency in the late winter. Obviously, any specific prophylactic measure which might lessen this burden will be well worth while.

THE VACCINE

There are two main antigens in the influenza virus, the soluble antigen and the hæmagglutinating antigen. The soluble antigen is stable and type-

specific and from it we can identify an influenza virus as belonging to types A, B or C. (Influenza virus C causes infection, often mild or inapparent, in young children.) The hæmagglutinating antigen is strain-specific and is liable to show antigenic variation, particularly in the case of influenza virus A. Minor variations occur quite often, and major changes occur at longer intervals. Since virus A was first discovered in 1933, two major variants have emerged: virus A1 (or A prime) in 1946-47, and A2 (or the Asian virus) in 1957. The latter strain was so different from its predecessors that previous infection with earlier A viruses did not seem to give any protection, and this was probably a major factor in the pandemic spread of this new variant. Obviously therefore virus A vaccines should contain the currently prevalent strain.

In the case of virus B, there has been a more gradual change in the antigenic make-up since 1940, but of a sufficient degree to render vaccines from the earlier Lee strain ineffective in protection against the current strains. In the light of evidence that there may be only a limited number of the hæmagglutinating antigenic components in virus A and that most strains carry them in varying degrees of dominance, some American workers believe that a polyvalent A vaccine can be used to give protection against infection with any influenza A variant. British experience does not support this belief.

When it was found that the influenza virus could be adapted to grow readily in the allantoic cavity of the chick embryo, the manufacture of influenza vaccines on a considerable scale became a practical possibility. Newly isolated strains have to be adapted by frequent passage to grow freely in the allantoic cavity. When fully adapted, enough virus can be obtained from one egg for 5 to 10 doses of virus vaccine containing 10,000 to 20,000 hæmagglutinating units per dose, which is roughly equivalent to 250 to 500 CCA units used in American vaccines. The virus vaccine is inactivated with formalin and is absorbed on to aluminium phosphate. For routine use, a mixed A and B virus vaccine is prepared and 1 ml. of the mixture is given by deep subcutaneous injection. The dose for children should be adjusted for age or weight. Moderate to severe local reactions—swelling and erythema —may occur in 2 to 4 per cent. of the inoculated and general reactions in 1 to 2 per cent. The vaccine should not be given to persons who are known to be egg-sensitive. Since influenza outbreaks occur mostly in the early months of the year, inoculations should be done during November or December. An adequate dose given in one injection should give increased protection for one year.

The use of vaccine suspended in an oil-emulsion has been tested in pilot trials in the United Kingdom and more extensively in the United States of America. The advantages are that only one-tenth of the dose of a saline vaccine is required to give an antibody response which is greater and lasts much longer than is the case with the saline vaccine. It should be noted,

however, that persistence of measurable antibodies is not necessarily correlated with clinical protection. Immediate local or general reactions are less common with oil-emulsion vaccine than occur with the saline vaccine, but in a few instances (0.1 to 0.5 per cent.) there have been delayed local reactions,

	No. at risk	No. admitted	Admission rate	No. of isolations / No. swabbed
Uninoculated	344	68	20%	40/55 | 44
Inoculated 1954 only	120	14	12%	4/12 | 67
„ 1955 „	100	8	8%	0/4 | 0
„ 1954 and 1955	100	2	2%	0/2 | 6

TABLE I.—Effect of immunization on admission for influenza to a residential-school sanatorium. (Modified from Hawkins *et al.*, 1956.)

characterized by persistent nodules and followed sometimes by tissue necrosis requiring surgical treatment (M.R.C., 1957). Further studies with different oil-emulsion adjuvants are in progress.

In the U.S.S.R. there has been an extensive experience in the use of living attenuated virus vaccines which are applied (by spraying or insufflation) to the nasal mucosa where the virus multiplies and stimulates antibody production. Simultaneous administration of A and B vaccines by this route is not recommended; one vaccine is given at least two weeks after the other.

CLINICAL TRIALS

Since 1951, a committee of the Medical Research Council has organized a series of serological and controlled clinical trials in human volunteers. These trials have been carried out in industrial communities, hospitals, universities, the fighting services, schools, and hostels. Groups varying from a few hundred for the assay of antibody responses up to 12,000 for the field trials have been used in successive trials, using a variety of vaccines. Initially the control groups were given a bacterial vaccine but in later trials different virus A and B vaccines have been used on comparable groups of volunteers. The over-all results have shown a reduction in sickness absenteeism of the order of 35 to 40 per cent. among those vaccinated against the prevalent virus infection, compared with the control groups. These rather disappointing findings may be due to either (a) the failure of killed vaccine, despite its preparation in a manner and concentration which could probably

not be bettered, to give a high degree of protection against influenza; or (b) the method of assessment being incapable of measuring the true degree of protection against virus influenza. As already indicated, a clinical diagnosis of influenza is bound to be inaccurate because of the difficulties in

Vaccine	No. of boys inoculated	No. of cases			Cases as a percentage of those inoculated in each group		
		Days after inoculation			Days after inoculation		
		1-8	9-15	16 and over	1-8	9-15	16 and over
Asian	404	95	33	5	23.4	8.2	1.2
Polyvalent A (non-Asian)	437	101	107	14	23.1	24.5	3.2
Virus B	429	93	106	16	21.7	24.7	3.7

TABLE II.—Incidence of influenza in public schools, according to length of time after inoculation. (Modified from M.R.C. Report, 1958.)

differentiation from respiratory infections due to other viruses. In periods of time when an epidemic in a community is at its peak, or in outbreaks among semi-closed communities, a larger proportion of all the respiratory illnesses is likely to be due to virus influenza and in these circumstances a fairer assessment of the protective value of the vaccine may be obtained.

Thus, in one of the M.R.C. trials (M.R.C., 1957) the reduction in attack rate among the vaccinated during a six-week period of relatively high incidence of influenza was 50 per cent., compared with no reduction during the other nineteen weeks of observation, when there was relatively little influenza. A more striking example comes from the experience in a sharp outbreak of authenticated virus A influenza in a large residential school (Hawkins *et al.*, 1956). Although not a controlled trial in the orthodox sense, the population was sufficiently homogeneous to give significant meaning to the findings which are set out in table I. Compared with an attack rate of 20 per cent. among the uninoculated boys, the incidence was only 2 per cent. among boys who had been inoculated twice (fourteen months and three months respectively before the outbreak) and it varied from 8 to 12 per cent. among boys given one injection either three months or fourteen months before the outbreak. These findings suggest that two injections of an appropriate influenza virus vaccine at one year's interval will give a high degree of protection against the infection. Controlled trials of influenza virus vaccines among the fighting services of the United States have given ratios of 1:3 up to 1:12 in favour of the vaccinated groups, except in the year 1947, when the vaccine prepared from virus A strains gave no protection against the new A1 strain.

When it was realized in March, 1957, that an entirely new variant of influenza virus A was sweeping round the world, plans were quickly made by the M.R.C. committee on influenza virus vaccines to test the protective value of an A2 (Asian) virus vaccine. Epidemiological and immunological evidence indicated that the populations among whom the infection was spreading had no previous experience of this mutant. Pilot trials with the vaccine showed that one injection gave a poor antibody response, whereas a second injection three weeks later increased the antibody titre tenfold. It was therefore planned to give certain of the trial groups two doses of vaccine at a strength of 7000 H.U./ml. and to use a single dose of a stronger vaccine (20,000 H.U./ml.) in other groups. The epidemic wave spread so quickly through the country, however, that the plans were upset and in only a few of the field trials could a fair assessment be obtained. The most encouraging results came from a group of public schools where the boys received one injection of the stronger vaccine on reassembly after the summer vacation. Influenza struck a number of these schools about the time the boys received their inoculations and, as table II shows, the groups receiving the Asian virus vaccine developed a considerable degree of immunity about eight days after their injections, when the attack rate dropped abruptly to one-third of the incidence in the other two groups. It may be noted that a polyvalent A vaccine (without the Asian strain) gave no obvious protection (M.R.C., 1958).

INDICATIONS FOR IMMUNIZATION

Although uncomplicated influenza is not a serious infection, it may, because of its high attack rate, cause considerable dislocation of the public economy. Incidence tends to be highest among children and in semi-closed communities, e.g. hospitals, barracks, boarding schools. In older people, pregnant women and in patients with chronic bronchitis, cardiovascular disease and diabetes mellitus, secondary bacterial complications such as bronchitis and broncho-pneumonia may cause severe illness and many deaths. The most serious of these complications is staphylococcal pneumonia which in the recent Asian influenza epidemic was responsible for about 60 per cent. of the fatal cases. Many staphylococcal infections occur among hospitalized patients and in such cases the infecting staphylococcus is often penicillin-resistant. For the family doctor already heavily overburdened during an epidemic, the temptation to refer elderly patients to hospital must be great but should, if circumstances permit, be resisted unless the patient obviously needs hospital treatment. Certainly the danger to life following an attack of influenza is greatest for elderly debilitated persons and they should be a priority group for immunization on medical grounds. From the viewpoint of public welfare, medical and nursing staff should be protected, as should those concerned with public safety, transport and other public utilities. Highly trained service and civilian staff, such as air

crews, should also be immunized. The immunization of older school children, particularly in boarding schools, and students in hostels and training colleges, where attack rates may be very high, should be considered.

The vaccine should, of course, contain the currently prevalent strains of virus A and B but when new antigenic variants appear there may not be sufficient time to adapt the new strain to eggs and to prepare stocks of vaccine. The World Influenza Centre in London and the International Influenza Centre for the Americas act as clearing houses for the identification of strains from most parts of the world. Unfortunately, the recent pandemic began in China, which is not covered by the World Health Organization, and two valuable months were lost before the causative virus was identified as an entirely new variant. The likelihood of epidemics of either A or B is very hard to predict, although laboratory data such as the isolation of particular type strains in the late Spring and sample surveys of antibody levels in a cross-section of the community may serve as useful straws in the wind (McWilliam, 1959).

CONCLUSIONS

Influenza virus vaccines prepared from currently prevalent strains give a considerable degree of protection against virus influenza. In authenticated outbreaks, the attack rate among vaccinated volunteers has been reduced to about one-third of the incidence in comparable control groups following one injection of the vaccine. In industrial groups where the diagnosis of influenza will include respiratory infections not due to the influenza viruses a reduction of the order of 40 to 50 per cent. may be expected during epidemic periods.

Subcutaneous inoculations of 1 ml. of a monovalent or mixed A and B virus vaccine should be given in November or December to selected groups in the community, including doctors and nurses and staff concerned with public safety and public utilities. The vaccine will afford protection if given at least eight to ten days before exposure to infection.

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TYPHOID AND PARATYPHOID IMMUNIZATION

By F. D. SCHOFIELD, M.D., M.R.C.P., D.T.M. & H.
Director of Medical Research, Department of Public Health, Territory of Papua and New Guinea

The risk to an uninoculated person of contracting typhoid fever or paratyphoid fever, and the medical facilities available, will vary greatly between different parts of the world and between different socio-economic conditions of life. These are the most important factors to assess before deciding whether or not to recommend a course of prophylactic vaccine. The discomfort and inconvenience of the reactions that follow the inoculations must also be taken into account. In addition, as the degrees of immunity produced by most vaccines have not yet been accurately determined, some knowledge is needed of past and present opinion on their relative efficacies.

GENERAL CONSIDERATIONS

Eight years after the first typhoid vaccines had been introduced (Pfeiffer and Kolle, 1896; Wright and Semple, 1897) Wright (1904) summarized in *The Practitioner* the experiences of Army and civilian doctors in the use of his heat-killed vaccine. It was thought to have reduced by half both the expected case incidence of typhoid fever and the expected case mortality—thus producing an apparent four-fold reduction in the death rate from the disease. Karl Pearson (1904) challenged the validity of these conclusions but, after intensive work in the laboratory and the field by an Antityphoid Committee (Report, 1913), the British Army officially adopted immunization. Boyd (1943), although unable to report a fully controlled field trial, studied the incidence among Allied and enemy troops in the Western Desert campaigns in the last war and provided good reasons for the belief that the British troops had received substantial protection from the heat-killed phenolized vaccine that was used in the Army until 1944. Cockburn (1955) pointed out that a strictly controlled field trial was very difficult to organize and that in fact none had yet been undertaken, but the results of such a trial were later reported from Yugoslavia by the WHO (1957).

This trial provided evidence that an alcoholized vaccine had little protective effect but that a heat-killed phenol-preserved vaccine gave about 70 per cent. protection. Further follow-up to the end of 1958 has shown that there appears to be a continuing degree of protection of the same order of magnitude as that observed during the first year after vaccination (Payne, 1959). The other conclusions reached were:—

The results found did not necessarily mean that an equal degree of protection could be obtained with other batches of phenolized vaccine in other circumstances. There was no reason to believe that the scheme of injections at present in use will

give the best results. The phenolized vaccine was to be preferred not only because of its greater protectiveness but also because it can be applied in the field without refrigeration. The existing laboratory tests (Widal and Vi agglutinations) could not be correlated with the protection afforded to man. A great deal more work, including strictly controlled tests in the field, was needed to determine what is the protective antibody in typhoid fever and what are the most effective antigenic preparations and the optimal method of their use.

All authorities are agreed that improved sanitation, especially the provision of safe water supplies, has made the greatest contribution to bringing typhoid fever under control.

Evidence in respect of the efficacy of paratyphoid vaccines is meagre; these vaccines are advocated more upon grounds of inference than upon reliable statistical studies. If typhoid vaccine is accepted it seems reasonable to accept paratyphoid vaccines also, and the addition of the latter does not seem to aggravate materially the reactions that follow the injections. The mixed vaccines are known as T.A.B. for convenience. There is no evidence that they diminish the severity of a clinical attack of one of the enteric fevers in a patient who has happened to contract the infection in spite of the inoculations.

A recent T.A.B. inoculation does not exclude the possibility of typhoid or paratyphoid in any case of undiagnosed fever. T.A.B. will usually have produced a moderate rise in H antibodies and only slight or no rise in O antibodies. In the case of an inoculated person the diagnosis of typhoid or paratyphoid fever can be suspected on serological grounds only if a rise in the titre of the specific O antibody occurs during the illness. A rise in H antibody alone is less significant as this may be due to an anamnestic reaction in response to other infections.

INDICATIONS AND CONTRAINDICATIONS

In Britain and in many other countries where sanitary conditions are comparatively good the enteric fevers are rare, and treatment with chloramphenicol has so reduced their mortality that inoculation of the general population is not warranted. It is justifiable, however, to immunize people at special risk such as nurses and other workers in fever hospitals.

Vaccine given to an individual who is actually incubating an enteric fever might increase the severity of his clinical attack (Wilson and Miles, 1955), but it is sometimes administered after the first bout of fever has subsided in the belief that it will decrease the incidence or diminish the severity of relapses. Patients who are treated with chloramphenicol early in the disease often fail to show the high rising agglutination titres in the Widal reaction that used to be seen in the days before antibiotics, but the vaccine is given to increase immunity; to produce an increase in agglutination titres is not the same thing.

The enteric fevers are much commoner in most tropical and subtropical countries than they are in Britain. Travellers to, or residents of, those countries should be advised in their own interest to be inoculated but this is not a compulsory requirement anywhere in the world.

The febrile reaction that follows the inoculation is often quite severe. This makes it unwise, in most circumstances, to inoculate pregnant women, very old people and anyone who is infirm or ill; and babies under one year old do not need inoculation because they do not contract the enteric fevers. It is widely believed that a patient with quiescent or recently active tuberculosis should not be given the vaccine as there is a danger that it might reactivate this infection. The doctor will often need to use his own clinical judgment of a patient's general state of health. When in doubt he is probably wise to withhold these inoculations.

THE VACCINES AND THEIR ADMINISTRATION

A phenolized vaccine known as T.A.B.C. is now in general use in Britain. It contains 1000 million heat-killed *Salmonella typhi* and 500 million each of *S. paratyphi A*, *B* and *C* per millilitre, supplied in containers of 1.5 ml., 10 ml., and 25 ml. It is best stored in a refrigerator at 2° to 4° C., but if this is not possible it must be stored in the dark above freezing point and below 10° C.

For a man over 140 pounds (63 kg.) in weight the first injection should measure 0.5 ml. The second injection, of 1 ml., is preferably given twenty-eight days later but this interval may, if necessary, be reduced to not less than seven days. When possible a third dose, of 1 ml., is given about six months after the second injection. Reinforcing 'booster' doses, to keep up immunity already acquired, should be of the same volume as the first dose, unless given intradermally. They are given at yearly intervals if possible but it is still satisfactory to give them within two years of the last inoculation. If no T.A.B. inoculations have been received for more than two years the primary course must be repeated in full. Women, men under 63 kg. in weight, and children over 12 years old are usually given four-fifths of this dosage (i.e. 0.4, 0.8 and 0.8 ml.). Children from 5 to 12 years old receive 0.2, 0.4 and 0.2 ml., and children from 1 to 5 years old should be given only 0.1, 0.2 and 0.1 ml.

People travelling to India or farther East may conveniently be given a mixed enteric and cholera vaccine—T.A.B. and cholera—for their primary course, particularly when a certificate of inoculation against cholera is a compulsory requirement for travel in that part of the world. The regulations concerning reimmunization against cholera, however, will not necessarily be appropriate in the case of reinforcing injections of T.A.B.

Tetanus toxoid can also be mixed with T.A.B.; this vaccine is called T.A.B.T. According to McLean and Holt (1940), tetanus toxoid given with T.A.B. stimulates a level of tetanus antitoxin about five times greater than that which follows tetanus toxoid given alone. The dosage of T.A.B. and cholera is the same as that of T.A.B.C. but with T.A.B.T. the volumes and intervals are different. There are two different strengths of T.A.B.T., arranged so that the 'first dose' of 1 ml. is equivalent in its bacterial count to

0.5 ml. of T.A.B. and the 'second dose', also of 1 ml., is equivalent to 1 ml. of T.A.B. There should be an interval of at least one month between these first two injections of T.A.B.T. For reinforcing 'booster' purposes 1 ml. of the 'first dose' strength should be given subcutaneously every year. Children aged 10 to 16 years are given two-thirds of adult doses, children aged 7 to 10 years one-half of adult doses. Children under 7 years old should be given T.A.B.C. and tetanus toxoid separately, because less than 0.5 ml. of T.A.B.T. is not sufficient to immunize them effectively against tetanus.

Before the injection the skin over the left upper arm (of a right-handed person) is cleaned with solvent ether. The injections used to be given intramuscularly into the left deltoid muscle but recently, for the primary course, subcutaneous injections have become routine because the least sensitivity to subsequent inoculations is produced by this method. For reinforcing doses of T.A.B.C. a technique said to be effective antigenically and to reduce reactions is to inject 0.1 ml. intradermally just behind the posterior border of the distal portion of the deltoid. T.A.B. is given in the afternoon whenever possible so that the recipients can then rest. They are advised to avoid alcohol for twenty-four hours because it aggravates the headache which often follows the injections.

Any of the T.A.B. group of vaccines may be administered at the same time as any other immunization procedures are undertaken except that against poliomyelitis. (No other vaccine should be given for two weeks before or after poliomyelitis inoculations). The inoculator should make out two copies of an inoculation certificate, each giving the name, quantity and batch number of each dose of the vaccine, the date, the patient's name, and the inoculator's name and address. One copy is given to the patient. There is no international certificate for T.A.B.C. or T.A.B.T. and when 'T.A.B. and cholera' is given an official international certificate is required for the cholera only; the T.A.B. should not be entered on the cholera certificate.

REACTIONS

Local redness, swelling, pain and tenderness at the site of injection appear in two or three hours. Various systemic symptoms such as malaise, headache, fever and nausea occur during the first twenty-four to thirty-six hours. These are all included in the term 'immediate reactions' and are common, both in the primary course and after reinforcing doses. The patient should be warned about them so that he will not be alarmed when they occur and so that he can make arrangements to prevent them interfering too much with his work or appointments.

Severe neurological disorders which have been found very occasionally shortly after T.A.B. inoculations are thought to be due to anaphylactic hypersensitivity (Miller and Stanton, 1954). The inoculations have been blamed for producing or precipitating the onset of many pathological conditions but the evidence for a causal connexion has not been substantiated statistically. In fact, a recent study on this subject in the R.A F. (Knox and

Stamm, 1957) provides evidence that if T.A.B. ever causes such disorders it must be extremely rare. These authors found that 'unit medical officers were all too ready to ascribe miscellaneous morbid conditions to inoculations'.

They compared a group, inoculated with a primary course of T.A.B.T., of about 27,000 men and 800 women with an uninoculated control group of about the same size. There was no increased incidence of collagen disease, encephalitis, poliomyelitis, meningitis or peripheral neuritis in the vaccinated group over a period of eight weeks' observation. There was a significantly greater incidence of upper-respiratory-tract infections in the control group. One per cent. of the vaccinated group was admitted to sick bay because of the severity of the immediate reactions and there was no difference in respect of these reactions between people given subcutaneous and people given intramuscular T.A.B.T.

It must be emphasized that these subjects were Service recruits and were therefore likely to have been exceptionally healthy when inoculated. The findings in this very useful study do not alter the categories already described of people to whom the vaccines should not be given.

CONCLUSION

Modern heat-killed phenol-preserved T.A.B. vaccines appear to confer a partial immunity against typhoid fever, but their protective effect against the paratyphoid fevers has not yet been demonstrated. At present only these vaccines should be given because there is not enough evidence on the immunizing properties of vaccines prepared by other methods.

The inoculations are recommended for people travelling to or living in the tropics and subtropics, but in Britain only individuals at special risk need immunization. Certificates of inoculation are not a compulsory requirement anywhere in the world.

Infants, pregnant women, very old people, invalids and anyone suspected of having active or quiescent tuberculosis should not be inoculated.

The recipients should be warned that unpleasant but transient local and general reactions are common during the first thirty-six hours after each injection. There is little reason to fear that T.A.B. will produce any serious long-term ill effects provided it is given only to healthy people.

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VACCINATION AGAINST YELLOW FEVER AND CHOLERA

By G. W. A. DICK, M.D., D.Sc., F.R.C.P.Ed.
Professor of Microbiology, Queen's University, Belfast

Yellow fever occurs in Africa and in the Americas. The endemic zone in Africa stretches from Dakar through French West Africa and the Sudan to Eritrea; the southern boundary is approximately the 15° parallel from Angola to Tanganyika. In the Americas yellow fever has occurred recently as far north as Guatemala and the endemic zone includes the major part of the Amazon and Orinoco basins, most of Colombia and stretches southwards to the state of Sao Paulo in Brazil. The virus of yellow fever is transmitted to man by the bite of infected mosquitoes. Prevention of yellow fever depends not only on control or eradication of the vectors but also on vaccination, particularly in rural areas where mosquito control is impracticable or impossible.

VACCINATION AGAINST YELLOW FEVER

Vaccination is required not only for the inhabitants of the endemic zones and for travellers going to these areas, but, in addition, many countries outside the endemic areas require that travellers who have come from or have passed through yellow fever areas shall have a valid certificate of vaccination against yellow fever. The form of International Certificate of Vaccination as specified in the International Sanitary Regulations (WHO, 1957) is the only acceptable certificate for international travel. It can usually be obtained from travel agencies, and failure to comply strictly with regulations relating to these certificates may cause great inconvenience or detention of travellers in certain countries. For most countries yellow fever vaccination certificates are valid ten days after the first vaccination has been done and thereafter for six years. On revaccination within six years the certificate is immediately valid and again lasts for six years. Most countries exclude infants up to six months or one year from yellow fever vaccination certificate requirements and, because of possible complications of vaccination of infants, it should be postponed where possible until the infant is at least nine months of age.

YELLOW FEVER VACCINES

There are two main types of vaccine: the 17D chick-embryo vaccine which is routinely administered by subcutaneous inoculation, and the French neurotropic mouse-brain vaccine which (as used at present by the French) consists of applying the vaccine to the scarified skin. Although the French neurotropic vaccine is a better antigen than 17D virus it carries certain risks and will not be considered further. 17D mouse-brain virus vaccine (Cannon

and Dewhurst, 1955; Meers, 1957) may prove safer than the French neurotropic vaccine for mass immunization by scarification.

The effectiveness of yellow fever vaccine is based on the demonstration that neutralizing antibodies develop after vaccination and, although no controlled field trial of yellow fever vaccine has been done, the absence of yellow fever in individuals vaccinated with potent vaccine in the field and in the laboratory is evidence of its efficacy.

17D vaccine.—After prolonged cultivation of virulent yellow fever virus in tissue culture a modification of the virus occurred and this modified or attenuated virus (17D) was adapted to grow in the developing embryos of hen eggs (Theiler and Smith, 1937).

In order to maintain uniformity and safety in vaccine production a primary seed lot of virus is prepared and from this a number of secondary seed lots which, having passed satisfactory monkey and safety tests, are reserved exclusively for vaccine production (Penna, 1956). In the manufacture of vaccine, developing chick embryos are inoculated with seed virus and the eggs are then incubated for four days when the embryos are removed from the eggs and ground up with sterile distilled water in Waring blenders. The egg pulp is tested for bacterial sterility, distributed in ampoules, freeze-dried *in vacuo*, and tested for potency. International regulations (WHO, 1945) require that the vaccine must contain not less than 150,000 mouse intracerebral LD50 doses per ml. of vaccine at the time of passing the manufacturers' potency tests and the minimal inoculation for man has been set at 500 LD50 although successful immunization can be achieved with very much smaller doses (Fox *et al.*, 1943; Dick and Horgan, 1952).

Because of the instability of yellow fever virus the vaccine must be transported under conditions which ensure a temperature constantly below 0° C., and after distribution it should be stored in a refrigerator below 5° C. Even with adequate storage yellow fever vaccine slowly drops in potency and each ampoule has a given expiry date, beyond which the vaccine should not be used.

Immediately before use the dried vaccine is reconstituted with cold sterile physiological saline or sterile water, and a single dose of 0.5 ml. is injected subcutaneously. Any reconstituted vaccine which is not used within half an hour should be discarded.

It has been shown that after subcutaneous injection of potent vaccine antibody develops within seven to ten days (Smithburn and Mahaffey, 1945). In laboratory controlled studies the antibody response has been observed in 100 per cent. of vaccinated individuals (Dick, 1952; Smithburn, 1956). Occasional failures occur under field conditions which are probably due to vaccine of inadequate potency or to faulty technique in its administration (Smithburn, 1956).

In order to facilitate mass vaccination programmes the administration of 17D vaccine by scarification was investigated (Hahn, 1951; Dick, 1952, 1956). Preliminary trials showed that the scarification technique was a less efficient method of immunization than when the vaccine was inoculated subcutaneously (Dick, 1952). This was confirmed by Cannon and Dewhurst (1953, 1955), who also prepared and tested a preparation of 17D mouse-brain vaccine for administration by scarification. A summary and discussion

of trials of the scarification technique has been presented by Meers (1957) who claims that 85 ± 5 per cent. of persons vaccinated by this method are solidly protected against yellow fever. Kerr (1957) is of the opinion that there 'seems to be nothing so good as the scarification technique for use in a house-to-house vaccination programme of rural people'. At the same time he points out that while a herd immunity of 85 per cent. would be reasonably satisfactory in a population exposed to the risk of epidemic infection it is not applicable to rural populations in the New World where an individual as well as a herd immunity is important (see also Meers, 1958).

POST-VACCINATION REACTIONS

The reactions to 17D vaccine by injection may be local, general, allergic or involve the central nervous system. Very rarely some slight redness occurs at the inoculation site, but otherwise local reactions do not occur. Apart from one outbreak of encephalitis in South America (Fox *et al.*, 1942) the general post-vaccination reactions to 17D chick-embryo vaccine are mild. Malaise, headache, backache and low-grade fever lasting from a few hours to a few days affect 10 to 15 per cent. of those vaccinated (Smith *et al.*, 1938). Only very rarely are these reactions severe enough to cause loss of time from normal duties. No severe reactions have been observed after scarification with 17D chick-embryo vaccine. Allergic reactions following vaccination are said to be rare, but can occur (Kouwenaar, 1953; Panthier and Husson, 1957) and patients submitting themselves for immunization should be questioned about allergies and appropriate preventive measures taken.

Up to 1940 no nervous reactions which could be attributed to vaccination are recorded in the literature. In 1941, an outbreak of encephalitis occurred following the use of a vaccine which had been prepared from virus which had been given a small number of subcultures from the seed virus (Fox *et al.*, 1942). This led to the use of primary and secondary seed lots of virus for vaccine production which has been mentioned and no cases of encephalitis in vaccinees were reported until 1953. Since then nine cases of meningo-encephalitis have been reported in infants less than eight months of age, all of whom recovered (Stuart, 1956; see also Panthier, 1956). In addition, two cases of encephalitis have been reported following vaccination with 17D vaccine and smallpox (Dick and Horgan, 1952), but it cannot be stated whether this might not have occurred if smallpox vaccine had been given alone.

COMBINED YELLOW FEVER AND SMALLPOX VACCINES

Combined 17D yellow fever and vaccinia vaccines administered by scarification were investigated by Hahn (1951) and by Dick and Horgan (1952). Hahn reported that twelve out of twelve persons previously unprotected against yellow fever were successfully immunized by this method. Dick and Horgan, however, found that only fourteen of twenty-one (67 per cent.)

unprotected persons were successfully immunized by the combined vaccine and Meers (1959) has recently confirmed their findings. The mixed vaccine in its present state does not produce a sufficiently high immunity rate against yellow fever to justify its use. No severe reactions followed the use of these combined vaccines.

It should be noted, however, that it has been recommended:

'(1) That, whenever possible, yellow fever inoculation should precede primary vaccination against smallpox, (2) that there should be an interval of at least four days between yellow fever inoculation (when given first) and primary vaccination against smallpox (when given subsequently), (3) that, if primary vaccination against smallpox is done first, there should be an interval of 21 days from the date of the vaccination before the yellow fever inoculation is given. (When infants under the age of 9 months are to be vaccinated against both yellow fever and smallpox, there should be an interval of 21 days between the two vaccinations, no matter which is performed first), and (4) that where there is evidence of previous successful vaccination against smallpox, yellow fever immunization and re-vaccination against smallpox may be carried out at the same session, but, if time permits, yellow fever immunization should always precede re-vaccination by at least four days'. (Ministry of Health, 1949.)

DURATION OF IMMUNITY OF YELLOW FEVER VACCINATION

Dick and Smithburn (1949) published the results of a post-vaccination survey of immunity which they carried out in an area of Uganda where yellow fever was not known to have occurred. They sampled groups of individuals who had presumably been vaccinated during a mass vaccination campaign five and six years before, and showed that the immunity rates were 83.8 and 87.4 per cent. five and six years after vaccination. As non-vaccinated controls they tested sera from children born into the area after the vaccination campaign and none of these had yellow fever antibody. In another study made in 1950, Dick and Gee (1952) showed that antibody was probably durable up to at least nine years after vaccination in the case of all persons who were seven years and over when vaccinated. A difference was noted in the immunity rates in the samples of children aged 9 to 15 years (63 per cent.) as compared with that of adult females aged 16 years and over (83 per cent.). Although Dick and Gee concluded that it seemed more likely that this difference was due to an excess of non-vaccinated children having been included in one of the samples it could also indicate a difference in response of young children, as compared with older children and adults, to vaccination as previously suggested by Fox and Cabral (1943).

At the time these antibody surveys of immunity were done the crossing and synergism which exists between yellow fever virus and other arbor viruses (Casals, 1957; Gordon Smith, 1958) was not known. Although subsequent studies (Manso de Souza, 1953; Courtois, 1954) have confirmed and extended Dick and Gee's observation, it would now appear that valid evidence of the durability of yellow fever immunity as measured by antibody must be made in areas not only where there is no yellow fever but also where viruses antigenically related to yellow fever are not present.

CHOLERA

With the exception of Russia where cholera was recorded in 1926, Iraq (1931), Iran (1939), Afghanistan (1946), Egypt (1947) and Syria (1948) cholera has remained restricted to India and countries to the east of it since 1923 (Swaroop and Pollitzer, 1955), and the insular countries of Asia have been virtually free from cholera since the end of the 1939-45 War. The chief endemic foci of cholera are in India, Pakistan and Burma, and the largest of these foci are in Bengal and in the delta region of the Ganges and Brahmaputra extending eastwards and westwards. East of India, cholera appears to have disappeared from China since 1948 and it is said not to be endemic there; Thailand and Indo-China and Cochin-China are endemic areas or are subject to importation of cholera from the chief endemic foci (Swaroop and Pollitzer, 1955).

The causative organism—the comma bacillus or *Vibrio choleræ*—has no host other than man and is transmitted mainly by contaminated water or food. The spread of the disease from place to place is by case or carrier infection and the most important way this occurs is by the mass movements of people on pilgrimages or to attend fairs.

Prevention of cholera depends, first, upon environmental sanitation. The most important preventive measures are the provision of permanently safe water supplies, safe methods of excreta disposal and safeguarding of the sale of food and drink—all problems of great difficulty in many eastern countries—and secondly on vaccination.

VACCINATION AGAINST CHOLERA

Travellers should not consider that having been vaccinated against cholera they can then disregard the hygiene of their immediate environment, particularly with regard to what they drink and eat. Vaccination against cholera does not produce the same complete measure of protection against cholera as does yellow fever vaccination against yellow fever, and vaccination should not be regarded as a substitute for sanitation.

Pollitzer (1957) has reviewed the evidence on the value of parenteral cholera immunization and feels convinced that 'though far from being a panacea, [it] is of great value for the prevention and control of manifestations of the disease'. Rogers (1957) is of the opinion that vaccination has clearly reduced the mortality from cholera in India during the past decade and 'all the evidence indicates that the cholera incidence in India as a whole is gradually being brought under control by the compulsory inoculation of . . . pilgrims'.

At the same time few field trials with cholera vaccines can stand up to critical statistical analysis and they do not provide a measure of the efficacy of the vaccines. Furthermore there would appear to be some doubt on the value of laboratory tests as a measure of immunity.

Vaccination is required for travellers going to countries where cholera is endemic or for travellers who have been in or have passed through countries where cholera occurs. Cholera vaccination certificates are valid for a period of six months beginning six days after the first injection of the vaccine or

on the date of re-vaccination within the six-months' period, and for a further six months thereafter. In most parts of the world infants under six months of age or one year do not require cholera vaccination certificates. The signature on all international cholera certificates must be *authenticated* by the medical officer of health of the area where vaccination was done.

CHOLERA VACCINES

Although various methods have been devised to produce active immunity against cholera, the only method which has been generally adopted is the parenteral administration of vaccines killed by heat and chemicals.

Of considerable importance in the preparation of the vaccines is the use of freshly isolated (and presumably virulent) strains. There has been discussion as to whether the vaccines should contain only *Vibrio choleræ* with the serological characters of O Group I sub-type Inaba or whether the sub-type Ogawa should be incorporated in the vaccines (see Pollitzer and Burrows, 1955). There is no clear agreement on the cross-protection which exists between the Ogawa and Inaba sub-types (Ranta and Dolman, 1944; Burrows *et al.*, 1947; Sokhey and Habbu, 1950) and for the present it would seem wise to incorporate both Inaba and Ogawa strains in vaccines.

The most widely used and tested vaccines are those based on the method introduced by Kolle in 1897: the vibrio are inoculated on to agar media and incubated for twenty-four hours at 37° C. The bacteria are washed off and inactivated usually with heat, and phenol is then added to give a final concentration of 0.5 per cent. and the vaccines are standardized by estimating the numbers of organisms per ml. Tests are made for bacterial sterility, absence of excessive toxicity and immunizing efficiency. During the last war, because of the shortage of agar, Sokhey and Habbu (1950) developed a fluid culture vaccine in which the Ogawa and Inaba sub-types of cholera vibrio were grown in a casein hydrolysate medium and inactivation carried out with formalin. Although these formolated vaccines have been used extensively in India since 1945 the results of field trials with them have not as far as is known been published.

In order to confer immunity it is essential to use a vaccine of sufficiently high titre, preferably one with a vibrio content of 8000 million organisms per ml. and it is generally recommended that the vaccine should be given in two doses of 0.5 ml. and 1 ml. respectively at an interval of seven to ten days (Pollitzer, 1957). It is possible that the spacing of the two doses might be increased with advantage. Under field conditions the two-dose system may not be possible, in which case a single 1 ml. injection is given. There is no negative phase after cholera immunization and immunity is established about seven days after immunization.

So far as children are concerned, Taylor (1951) is of the opinion that children under one year should not be vaccinated. The British Army authorities are of the same opinion and recommend that children of one to five years should be given 0.25 ml. for the first dose and 0.5 ml. for the second (Memorandum, 1956).

Cholera vaccine does not appear to deteriorate greatly on storage, even at temperatures of 37° C. or more (Maitra and Ahuja, 1932; Taylor *et al.*, 1936) and it would appear unnecessary to take special precautions for its preservation although storage in a refrigerator would seem to be preferable. Administration of the vaccine by the intradermal technique was investi-

gated by Panja and Das (1947) and Singer *et al.* (1948), who found that higher or equally satisfactory levels of antibody occurred by this route as compared with subcutaneous inoculation. It is doubtful if this method could be used for mass immunization, in spite of the great saving in vaccine which would result. It is, however, the method recommended in Malaya.

Cholera vaccine may also be obtained combined with typhoid-paratyphoid A and B. There is little field experience with this combined vaccine but Manalang (1925) maintained that the combination of different vaccines had an enhancing effect on the antigenicity of each component. The reactions of this mixed vaccine, whilst not greater than those following T.A.B. vaccines, are greater than that of cholera vaccine. Whilst this might be of little importance in immunizing travellers who required both T.A.B. and cholera, 'the absence of marked reactions was instrumental in overcoming the prejudice against sole cholera vaccination in mass vaccination campaigns' (Pollitzer and Burrows, 1955).

POST-VACCINATION REACTIONS

As a rule 'the reaction either local or general produced by the vaccine is negligible and inoculated persons can carry on with their work' (Taylor, 1951). Occasionally the site of injection is painful and tender within the first twenty-four hours or about the eighth or fourteenth day after vaccination. A slight pyrexia may also be evident at these times. Lassitude, vomiting and diarrhœa occur in a few individuals. Woodward (1946) described a condition simulating appendicitis as a reaction of vaccination in 38 of 1,100 vaccinees.

DURATION OF IMMUNITY OF CHOLERA VACCINATION

General agreement exists that immunity is not established until about one week after vaccination. The immunity is of short duration and there is some difference of opinion as to how long it lasts. The best evidence on this was provided by Adiseshan *et al.* (1947), who showed that, in villages which had second outbreaks of cholera within six months of an epidemic, the incidence of cholera in those who had been vaccinated at the time of the initial outbreak was statistically lower than among non-vaccinated individuals. 'The protection afforded by anti-cholera inoculation continues, therefore, for at least six months'. In villages in which reinfections occurred six to twelve months after an outbreak when vaccinations were done, the virtual absence of cholera among vaccinated individuals suggested that immunity may last for as long as twelve months. It is difficult to ascertain how the possible protective effect of subclinical infections was excluded in these studies, and in spite of the millions of cholera inoculations which have been given there is a great lack of precise knowledge on the efficacy of this vaccine.

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A RATIONAL APPROACH TO THE MANAGEMENT OF EPISTAXIS

By R. J. BENNETT, M.B., F.R.C.S.

Senior Consulting Ear, Nose and Throat Surgeon, Durham and North-West Durham Groups of Hospitals

EPISTAXIS (επι above and στραξις dripping) is not a specific disease process, but is essentially a symptom complex. Thus, the blood, passing externally, usually presents as an obvious nose-bleed, although, on occasions, taking origin in the posterior parts of the nose, it may escape into the nasopharynx—its site of origin unsuspected and a hæmoptysis or a hæmatemesis incorrectly

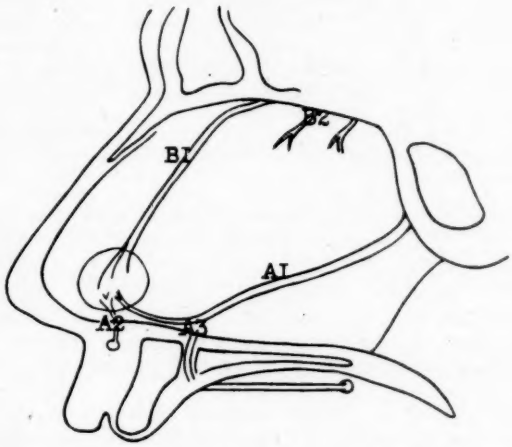

FIG. 1.—Arteries of the nasal septum. (For abbreviations see text.)

diagnosed. Epistaxis therefore poses both a diagnostic and a therapeutic problem, simple and straightforward in the vast majority of cases, but occasionally difficult of treatment or diagnosis unless the management of each case is individualized. There has been no sudden or revolutionary change in the clinical approach to nasal hæmorrhage, and our present methods of dealing with this problem have been gradually evolved as a result of a more exact knowledge of the pathological processes involved and by improvements in hæmostatic agents and surgical techniques.

SURGICAL ANATOMY

A knowledge of the relationship of the blood vessels to the nasal landmarks and their variable anastomotic communications is of importance in considering the means to be employed in stopping nasal bleeding. The arterial supply to the nasal structures derives from both the internal and external

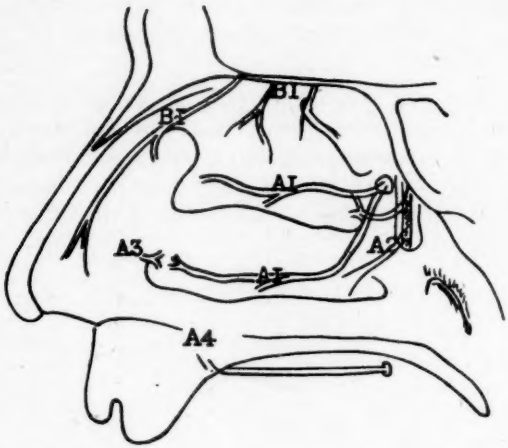

FIG. 2.—Arteries of the lateral nasal wall. (For abbreviations see text.)

carotid systems, the former supplying the antero-superior, the latter the postero-inferior portions. Although the main supply comes from the external carotid, both carotid arteries have numerous and free anastomotic channels both between themselves and with their fellows of the opposite side.

Arteries of the nasal septum (fig. 1).—(A) *From the external carotid artery:*

(1) The septal branch of the sphenopalatine artery from the maxillary artery.

(2) The septal branch of the superior labial artery from the facial artery.

(3) The septal branch of the greater palatine artery from the maxillary artery.

(B) *From the internal carotid artery:*

(1) The septal branch of the anterior ethmoidal artery from the ophthalmic artery.

(2) The septal branch of the posterior ethmoidal artery from the ophthalmic artery.

(C) *Little's area:*

Situated on the anterior septum is a vascular area which is supplied by the terminal twigs of the septal branches of the sphenopalatine, the greater palatine, the superior labial and the anterior and posterior ethmoidal arteries. It is a frequent site of nasal bleeding, especially in children and young adults and is known as Little's area.

Arteries of the lateral wall (fig. 2).—(A) *From the external carotid artery:*
(1) The middle and inferior turbinate branches of the sphenopalatine artery from the maxillary artery.
(2) The nasal branches of the greater palatine artery from the maxillary artery.
(3) The antero-inferior dental arteries from the infraorbital artery.
(4) The terminal branches of the greater palatine artery from the maxillary artery.

(B) *From the internal carotid artery:* (1) The anterior and posterior ethmoida arteries from the ophthalmic artery.

ETIOLOGY

(A) *Trauma:*
(1) Major trauma
- (a) Accidental
- (b) Deliberate—surgical
- (c) Deliberate—criminal assault
  self-inflicted—hysterics
  —malingerers

(2) Minor trauma
- (a) Violent nose blowing
- (b) Nose picking

(B) *Inflammatory lesions:*
(1) Specific systemic infections
- (a) The exanthemas: scarlet fever, measles, chickenpox, smallpox
- (b) Other specific systemic infections: typhoid fever, paratyphoid fever, pneumonia, infectious mononucleosis, whooping-cough

(2) Specific local infections
- (a) Specific nasal infections: nasal diphtheria, gumma of the nose
- (b) Non-specific nasal infections: the onset of acute upper respiratory tract infections; granuloma of the turbinates

(3) Local crusting lesions of the nose
- (a) Septal perforations with crusting
- (b) Atrophic rhinitis: primary form, secondary form due to syphilis, tuberculosis or rhinoscleroma

(4) Lesions producing local congestion in the nose
- (a) Mechanical factors: adenoids, deviated nasal septum, nasal polyps, foreign bodies in the nose
- (b) Chronic irritative lesions: chemical irritation, irradiation, excessive smoking

(C) *Alterations in the extra/intra blood-vessel pressure ratio:*
(1) High altitudes
(2) High intravascular pressures
- (a) Arterial: essential and secondary hypertension
- (b) Venous: temporary increase in venous pressure as in emphysema, whooping-cough and bronchitis; more permanent pressure changes as in tumours of the superior vena cava

(D) *Neoplasms of the nose:*
(1) Benign neoplasms: angioma (bleeding polyp of the septum)
(2) Malignant neoplasms: primary cancer of the nasal passages; secondary cancer invading the nose from nearby or distant sources

(E) *Diseases of the blood vessels:*
(1) Arteries: atherosclerosis with or without hypertension; rheumatic vascular disease
(2) Capillaries (both decreased capillary resistance and decreased capillary contractility): scurvy, congenital hæmorrhagic telangiectasia; primary or idiopathic thrombocytopenic purpura; secondary purpuras
(3) Veins: phlebosclerosis

(F) *Diseases of defective coagulation:*
(1) Hæmophilia
(2) Pseudohæmophilia
(3) Prothrombin deficiencies: faulty absorption of vitamin K as in sprue and intestinal fistulæ; cirrhosis of the liver; obstructive jaundice
(4) Christmas disease
(5) 'Factor VII' deficiencies: Dicoumarol and ethyl biscoumacetate therapy; excessive salicylates
(6) Congenital afibrinogenæmia
(7) Excessive heparin: heparin therapy
(8) Heparinoid states (due to the presence of a heparin-like substance): leukæmia; aplastic anæmia; lymphosarcoma; multiple myeloma; Hodgkin's disease; pernicious anæmia
(9) Polycythæmia vera rubra

(G) *Functional and hysterical states*

(H) *Hormonal factors:*
(1) Vicarious menstruation
(2) The epistaxis of pregnancy

(I) *Bleeding originating outside the nasal cavities:*
(1) Nasopharyngeal neoplasms
(2) From the maxillary sinuses: trauma; antro-oral fistulæ after dental extraction; hyperplastic sinusitis
(3) Cancer of the sinuses
(4) From the other sinuses: erosion of an internal carotid aneurysm into the spheno-ethmoid sinuses.

MANAGEMENT

The multiplicity of causes, the various sites and the variable severity of nasal bleeding make it obvious that the management of epistaxis cannot be standardized, although the basic principles in the management of hæmorrhage have to be observed.

For practical clinical purposes, cases of epistaxis can be divided into two groups:—

(a) Cases of recurring, mild bleeding
(b) An actively bleeding case

THE MANAGEMENT OF RECURRING, MILD EPISTAXIS

These patients present with a history of one or previous episodes of bleeding, the bleeding invariably arising in Little's area, although on examination there may be no evidence of a bleeding point. The source of the bleeding can usually be found, however, if a determined attempt is made to find it, for the offending vessel is often betrayed by a clot plugging the site of rupture. Even in its absence the bleeding point can invariably be located by gently rubbing the mucous membrane of the anterior part of the nose with cotton-wool moistened in a solution of 5 per cent. cocaine hydrochloride. It is desirable to produce bleeding to be sure that the site of the hæmorrhage has been located, thus placing the case into the category of an active nosebleed with the accompanying appropriate treatment. Frequently, although no bleeding point is found, dilated superficial vessels are seen in Little's area leading one to suspect that this is the site of the hæmorrhage. If there

is any doubt as to the origin or cause of the epistaxis appropriate laboratory studies are indicated to exclude the bleeding being caused by some systemic disease, as in such cases treatment of the underlying disease is of paramount importance in addition to the more usual local measures.

THE MANAGEMENT OF ACTIVE EPISTAXIS

Whatever the cause or source of the hæmorrhage, the aim of treatment is to stop the bleeding as promptly as possible with the most conservative means that prove effective, although the method employed must vary according to the etiology and site and severity of the epistaxis. It is rarely that nasal hæmorrhage, whatever its site, cannot be controlled albeit temporarily while utilizing procedures directed to more permanent control. The accessibility of the bleeding site determines to a large extent the effectiveness with which hæmostasis can be applied. Thus, anterior bleeding is controlled much more readily than posterior bleeding, especially as the former type of bleeding is more commonly encountered in young individuals and is usually of capillary or veno-capillary type.

On admission to hospital the patient should be examined first for symptoms of shock and active hæmorrhage, always bearing in mind that the nausea produced by the swallowing of blood may superficially resemble a state of shock. Morphine and, if necessary, blood transfusions go a long way towards allaying the restlessness and anxiety of these patients; with slow drip techniques, it is unusual to cause a sudden rise in the blood pressure and thus further bleeding. In any case, since the hypertensive is physiologically adapted to his high blood pressure, it is this type of case which suffers most from prolonged hypotension, especially as their peripheral and coronary atherosclerosis predispose to thrombotic phenomena. As all elements of the blood are lost, replacement should be made with whole blood, since the use of substitutes results in the dilution of the red blood corpuscles with resulting anoxia.

In the absence of shock, the first step in treatment is the reassurance of the patient and his family—an end accomplished in the first instance by complete calm and assurance on the part of the examining surgeon. In all severe cases the administration of a sedative is indicated—opiates being ideal for this purpose, but care must be taken in a patient who has lost any appreciable amount of blood as usual doses of opiates may precipitate a state of shock.

On no account must the patient lie on his back, as the blood will fill his stomach and nauseate him. Ideally the patient should be propped up with pillows at an angle of 45 degrees or more. This reduces both the arterial and venous cephalic blood pressure and tends to minimize the severity of the bleeding. Naturally, this cannot be done if he is unconscious or so full of narcotics that he has lost his cough reflex. If a patient feels faint and has to lie down, he should be persuaded to lie on his side so that the blood

can run out of his nose in to a basin. If he has been involved in an accident with a suspected cerebral injury, opiates may well be contraindicated. If the hæmorrhage has been controlled by packs previously inserted they are left in place and the patient carefully watched for further bleeding.

When active bleeding is occurring, the packs are removed and the nose is cleared of clots, either by blowing or, better, by the use of a suction apparatus. Cotton-wool pledgets moistened in equal parts of 5 per cent. cocaine hydrochloride and 1:1000 solution of adrenaline are then used to shrink the mucous membrane and to produce local anæsthesia for any necessary manipulations and in an effort to locate the source of the bleeding. It is essential, however, that these pledgets of cocaine be well wrung out and do not contain any excess of cocaine, as a cocaine reaction is more liable to occur in those individuals who have lost blood.

In cases of active anterior nasal bleeding the bleeding area can usually be seen and, if the hæmorrhage is not too profuse, the bleeding can be stopped, and the mucous membrane anæsthetized at the same time, by alternate applications of 5 per cent. cocaine and 1:1000 adrenaline solution. Permanent control of the bleeding can then invariably be obtained by cauterization of the bleeding area. Chemical cautery is better in children and satisfactory in most adults, but it is essential to realize that chemical cauterizing agents are only effective when applied to a dry surface and not while there is active bleeding. If successful, the bleeding is now controlled and no packing is necessary, although for a week following cauterization it is advisable to use a simple ointment, such as white soft paraffin B.P., to the cauterized nostril as scabbing occurs and unless softened might irritate and result in nose picking with further epistaxes. If bleeding recurs, or continues, more efficient methods of obliterating the vascular area must be attempted. Galvanocautery applied to the septum in three linear applications, passing above, through and below the bleeding point, is probably the most effective of the more simple measures that can be attempted.

It often happens, especially in the hypertensive patient, that the bleeding is so severe and so difficult to locate, being posterior in site, that something has to be done at once. The nose is quickly packed under direct vision, care being taken not to traumatize the mucous membrane with the dressing forceps. The effectiveness of the nasal pack depends more upon the precision of its insertion and the firmness of its pressure than upon the nature of the packing agent. Control of the epistaxis is confirmed by looking into the mouth to make sure that no blood is running down the pharyngeal wall. The most satisfactory and the simplest pack is a 1-inch (2.5 cm.) ribbon gauze pressure pack, lubricated with sterile liquid paraffin or better still impregnated with bismuth and glycerin. In the more severe episodes of epistaxis, as a rule encountered in elderly individuals, the bleeding is such that it is not always controlled by the anterior pack and it becomes necessary to insert a posterior choanal plug. As this exerts pressure against the sphenopalatine artery on the floor of the sphenoid sinus and the septum,

to be of value it must be held securely in place. If the bleeding is still incompletely controlled an anterior gauze pack can be packed against the postnasal plug completely filling the affected nasal chamber. Where postnasal packing is used damage to the nasal floor or laceration of the soft palate may arise, the latter often occurring insidiously as a pressure effect of too tight a string passing from the pack out through the mouth. In these heavy bleeds, whichever type of pack has been used, it is usually left in place for from five to seven days; if the bleeding can be arrested completely for this period, sufficient healing takes place to make control permanent. Although the plugs smell rather badly after a few days this occasions no great harm but patients retaining nasal plugs for more than twenty-four hours should be given systemic antibiotic therapy. After four or five days' retention these packs are easy to remove being well lubricated by the nasal mucus; their removal rarely causes further bleeding at the end of this time and, surprisingly enough, the nasal membranes usually appear to be in very good condition.

It is advisable, and undoubtedly of value, to administer ascorbic acid as a routine to these patients, as deficiency of this vitamin has been shown to occur commonly in these patients.

It is rarely that these measures fail to control an epistaxis but occasionally a grossly deviated nasal septum will prevent efficient packing. In such cases a submucous resection of the nasal septum is done with posterior choanal plugs *in situ*. Occasionally, even in posterior bleeds, the bleeding point can be accurately located and, if there is enough room, the area can be cauterized with the galvanocautery. Alternatively, in such cases 'spot packing' with an absorbable sponge material can be used to control the bleeding.

ARTERIAL LIGATION

If bleeding recurs or continues in major degree after the nasal and postnasal packs have been in place twenty-four hours, it is useless and indeed dangerous to procrastinate further: ligation of a principal artery on the cardiac side of the rupture is a life-saving measure in these cases. In selecting the vessel to ligate it is well to remember the anatomy of the nasal blood supply. The use of the middle turbinate as a landmark is useful in establishing the source of the bleeding: bleeding above it is from a branch of the internal carotid artery whilst below it it is from the external carotid system. Occasionally the approximate source of the bleeding can be determined by observing the effect of packing different regions of the nasal cavity; digital pressure on the common carotid artery may be used as an additional aid. If compression of this artery considerably diminishes the severity of the hæmorrhage this would strongly suggest its origin from an ethmoidal artery.

There are several alternatives:—

Ligation of a main arterial source away from the site of rupture: i.e. the external carotid artery, the internal carotid artery, or the common carotid

artery. Ligation of the external carotid artery by diminishing the total blood flow through the nose is often a satisfactory method of controlling bleeding from the branches of this main arterial system. On the other hand, because of the efficiency of the circle of Willis, ligation of the internal or common carotid arteries does not usually control the hæmorrhage from the ethmoidal vessels. In fact if ligation of either of these two latter vessels were to succeed it would also be likely to produce serious cerebral damage—due to a poor anastomotic arrangement at the circle of Willis. Ligation of these vessels is therefore rarely justifiable except in those rare instances in which epistaxis may result from rupture of an intracranial aneurysm into an accessory air sinus.

Ligation of a branch near the site of rupture: i.e. the maxillary artery by the transantral approach, or the ethmoidal arteries. Ligation of a main branch on the cardiac side but near the point of rupture is an effective procedure and conforms with the surgical principles of terminal ligation of bleeding vessels. It affords an opportunity to cut off the arterial supply as close as possible to the site of hæmorrhage and thus obviates any intermediate branches.

Since bleeding can continue after ligation of the carotid vessels the logical method of controlling bleeding from the ethmoidal vessels is by ligating the vessels themselves in the orbit.

EPISTAXIS REQUIRING SPECIAL MEASURES FOR CONTROL

In traumatic cases, in which epistaxis may be complicated by fractures involving the cribriform plate, gauze packing is not only likely to prove ineffective in controlling the hæmorrhage, as the site of its origin is high in the narrow superior parts of the nasal cavities, but is actually dangerous because of the risk of producing a septic reaction and intracranial spread. In these cases 'spot packing' with an absorbable sponge packing saturated with thrombin and held in place with rubber or nylon sponge may prove useful. If simple measures do not rapidly prove effective, it is probably better to obliterate the ethmoidal arteries early.

In epistaxis due to multiple telangiectasia a temporary measure for immediate control by the patient is the intranasal auto-inflatable balloon, although more heroic measures are often required. Whilst little in the way of a permanent cure can be offered to these patients, the protracted use of rutin in doses of 300 mg. daily is of benefit, and dramatic results have been reported in refractory cases with the systemic use of œstrogens. Extensive electrocoagulation of the nasal membranes has been advocated (Figi and Watkins, 1943), whilst Crowe advocates a combination of *beta*-radiation and deep x-ray therapy. Repeated blood transfusions are often necessary to combat the anæmia resulting from the frequent hæmorrhages.

When epistaxis occurs in the blood dyscrasias, the bleeding tends to arise diffusely from the nasal membranes. In those dyscrasias due to defective

capillaries, simple measures such as the topical application of thrombin, thromboplastin or vasoconstrictors are usually effective and prevent the necessity for nasal packing, unless the bleeding is so severe that packing becomes necessary to save life. In this latter event an absorbable packing such as oxidised cellulose is better for it causes less trauma to the membranes than ribbon gauze and, being absorbable, does not require removal. Two words of warning must be expressed in the use of the absorbable sponge: in the first place the gauze must be placed lightly over the bleeding area; if it is tightly packed it causes necrosis of the mucous membrane. Secondly, chemical caustics should not be used first as they prevent absorption of the gauze. In the dyscrasias due to clotting abnormalities of the blood the principles of treatment are to supply the defective substances either by transfusion or by a fraction of the plasma if it is available. Fresh blood is always to be preferred to stored blood, the one exception being the hæmorrhagic state resulting from absence of the Christmas factor as this factor is stable on storage. In hæmorrhagic states due to excessive heparin therapy, the drug is immediately withdrawn and whole, fresh blood transfusions are given. Protamine sulphate in doses of 50 to 100 mg. is the specific antiheparin measure.

Cortisone and corticotrophin have been used, with remission of the hæmorrhagic symptoms, in idiopathic thrombocytopenic purpura, allergic purpura and pseudohæmophilia, presumably because of its effect in decreasing capillary fragility.

There are certain local conditions manifesting themselves by epistaxis that require special measures. For patients with anterior septal perforations or deviations with crusting and repeated bleedings, a modified submucous resection of the nasal septum with removal of the exposed cartilage around it is the treatment of choice and is usually effective. In cases of hæmangioma of the nasal septum, to prevent recurrence it is necessary to excise the lesion with a margin of healthy mucosa and to cauterize the exposed surface of the septum.

Occasionally bleeding arises from within the maxillary antrum; if it is not readily controlled by antral lavage a Caldwell Luc antrostomy becomes necessary.

This article is condensed from the prize-winning essay submitted to the Midland Institute of Otology.

I would like to thank Mr. C. Gill-Carey who not only allowed me to use his cases, but who also talked over some of his more difficult cases of epistaxis with me. My thanks are also due to Mr. J. C. Hogg who both allowed me to use his cases and who discussed in detail with me the management of some of his more refractory cases of epistaxis. I am also indebted to the following surgeons of the Royal National Throat, Nose and Ear Hospital: Mr. J. W. Cope, Mr. G. Howells and Mr. K. Rotter.

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KNOTTING IN MEDICINE AND SURGERY

By R. M. FLINN, M.B., Ch.B.
The Children's Hospital, Birmingham

The aim of this article is to present an account of the history and technique of knotting as applied to medicine and surgery. It was prompted by observation of many surgeons at work, and the difficulties which they encountered.

HISTORY

The association of knots with medicine and surgery extends far back into history. It was once believed that knots could cure human illness. For instance, a favourite way to get rid of warts in mediæval Germany, was to tie some knots in a piece of string, one for each wart, and then to leave the string under a stone. The first person to tread on the stone would gain the warts, and the original sufferer would be freed.

Zulu warriors tied a knot in the tail of every animal they killed as a charm against abdominal pain acquired after eating its flesh. All over the world similar knots have traditionally been used as protective amulets against all kinds of evil and danger. One superstition which has many variations throughout Europe is related to childbirth: pregnant women were forbidden to wear any knots or knotted garments, lest their delivery be obstructed. This belief was pressed into service throughout Scandinavia for the purposes of a primitive sort of birth control.

When two parents considered their offspring numerous enough, they would give the name 'Knut' (English Canute meaning knot) to the latest born boy, hoping thereby to prevent the conception of another child. A similar belief, common in Europe until the 18th century, was that certain magic knots could bewitch a bridegroom, and interfere with the consummation of a marriage. As late as 1705, two people were condemned to death in Scotland, for concealing in some clothing nine magic knots tied for the purpose of marring the wedded happiness of one, Spalding of Ashantilly.

The earliest analytical description of knots is found in 'Iatrikon Synagogos', a medical treatise compiled by Oribasius of Pergamum, in the 4th century A.D. Oribasius, a Greek, was court physician to the Emperor Julian, who died in A.D. 386. He copied his material from Heraklas, believed to be a contemporary or pupil of Heliodorus, a physician who flourished about A.D. 100. Oribasius confined himself to eighteen knots used as slings and ties by physicians. His familiarity with complex knots, and the numerous different ways of tying them, suggests that the art of knotting must have been highly developed in the profession in those days.

Between the time of Oribasius and the 19th century, literature on knotting is almost non-existent. During the past three hundred years there has been a migration of the art's master craftsmen from the medical profession to the sea.

THEORY AND TECHNIQUE

The actual number of knots used by the profession today is very small. Surgeons, like artists, seem to belong to two types, both equally competent. The first, the nimble intuitive mind, is almost always endowed with light sensitive hands and fingers. The second, the methodical reasoning mind, usually has heavy hands and fingers that are clumsy. The former will nearly always tie excellent knots; whilst the latter, having no particular aptitude for them, is apt to discount their importance. Little attention is given to the teaching of the anatomy and physiology of knots in our medical schools, yet it is a subject in which a firm groundwork can be gained in a short time.

SOME COMMON KNOTS

The most fundamental of all knots used in surgery is called the *half-knot*, of which there are two varieties (fig. 1). Most surgical knots are built up of a combination of these two, alone or with slight modification. These two knots can be tied either with two hands, a method which should not require further description here, or with one hand, as is most commonly seen. The single-handed method of tying knot (a) (fig. 1) is shown in fig. 2. Similarly, knot (b) is shown in fig. 3.

The *reef* or *square knot* has a characteristic shape (fig. 4). It lies snug and flat, with both of the loose ends on the same side of the knot, and pointing in exactly opposite directions. It is built up of knot (a) followed by knot (b), or vice versa. The reef knot is one of the most deceptive of all knots. Accurately tied and correctly applied, it is safe and secure. Misused it is very treacherous. It has been said that more deaths occur each year from the misuse of the reef knot, than from the failure of any other six knots put together. There are certain fundamental rules which must be taken into consideration when using the reef knot. First, it must always be used as a binder knot; that is, where the knot is in close contact with an object, as in tying a parcel. It should never lie loose, as, for instance, when two hawsers or climbing ropes are joined together. Secondly, the strain on the two ends must be continuous and not intermittent. Great care should be taken that the reef knot assumes the correct shape when tied, as will be shown later.

Figure 5 shows the *granny knot*, which is built up of two (a) knots or two (b) knots. It is an extremely unsafe knot, being very inclined to slip, and should be avoided at all costs unless suitable precautions are taken to prevent this occurrence. C. W. Mayo described the modification shown in fig. 6. Two identical half-knots are first tied, forming a granny knot. This permits of slight adjustment after the knot has been drawn up. When the tension has been adjusted, a third and opposite half-knot is added, forming a reef with the second half-knot. This locks the whole knot tight. The addition of a third half-knot to a well-tied reef knot is quite unnecessary. Provided the latter has been tied securely, the addition of any further half-knot only adds to the bulk, without materially increasing its strength.

There is a modification of the reef knot which is often seen in the operating

theatre. It is shown in fig. 7, and consists of a reef knot in which an extra tuck through has been made in the first half-knot. It is commonly called the *surgeon's knot*, and is certainly secure, particularly in materials which tend to slip when tied. It is, however, very ugly, and when drawn tight is

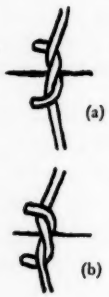

FIG. 1

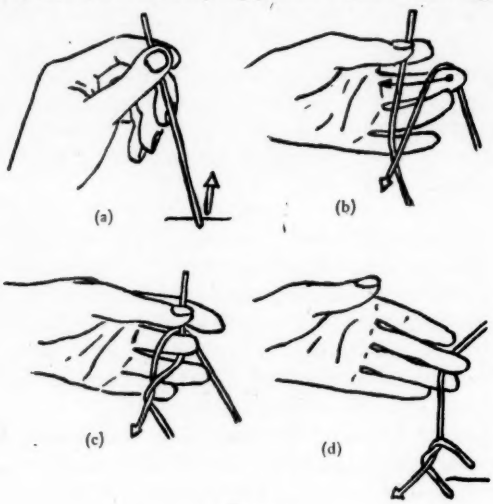

FIG. 2

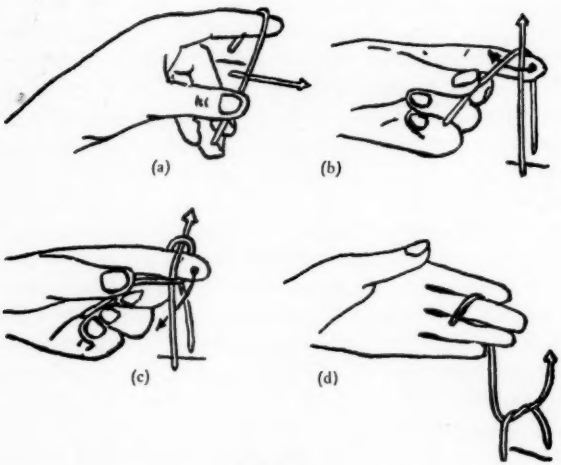

FIG. 3

bulky: a factor to be taken into account when using absorbable materials such as catgut.

The reef and granny knots appear to be easy knots to tie. In reality they are no such thing, for observation has shown that over half the knots

made in the theatre with a reef as the intention, are in actual fact not reefs at all. The motions of making the knot are performed correctly, but the result is not quite right. The reason for this is that both the reef and granny collapse extremely easily when the strain on the two ends is unequal, producing the knots shown in Fig. 8 and 9 respectively. Both these knots are insecure. This collapse is easily demonstrable with a short piece of string.

FIG. 4

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 9

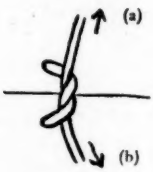

FIG. 10

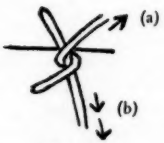

FIG. 11

FIG. 12

To tie the knot depicted in fig. 10, the strain on the two ends 'a' and 'b' must be exactly the same. If, for instance, 'b' is pulled a little tighter than 'a', fig. 11 results—a *half hitch*, which has no hold at all. This may occur at either of the two stages in the making of the knot. It is practically impossible to tie a reef knot single-handed if any appreciable tension is employed. For the same reason, holding the two free ends close together so that they may be cut short is liable to disrupt the knot (fig. 12). Inspection of a reef will show that the two free ends lie in opposite directions; any pull not in these directions will alter the shape of the knot. It is to prevent this occurring that some surgeons add a third half-knot. If this last half-knot were to collapse, the likelihood of the underlying reef doing so would be small.

Few people have any precise notions regarding the security and breaking strength of knots. Perhaps the commonest misconception is that a knot is weaker than the cord in which it is tied. It is almost unknown for a break to occur in a knot: it is always the cord that gives, usually at its junction with the knot. The force that makes knots hold is friction; hence there are two basic principles—first, that contiguous parts should move in opposite directions when tension is applied. For example, compare the

loosely tied reef in fig. 13 with the *thief knot* of similar appearance (fig. 14). When tension is applied to the ends, the 'thief' slides easily apart. The second principle is that the greater the tension, the more tightly should the parts be held or nipped together.

The *clove hitch* is a well-known knot (fig. 15) which, however, has a

FIG. 13

FIG. 14

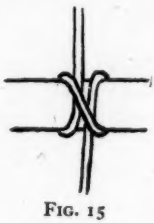

FIG. 15

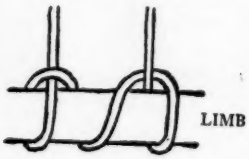

FIG. 16

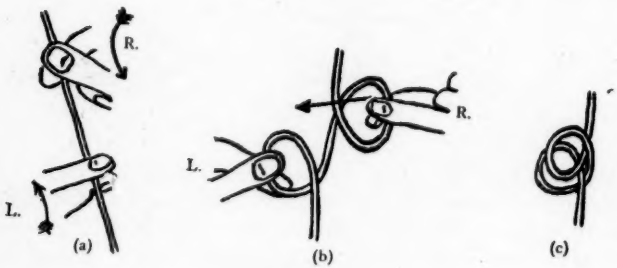

FIG. 17

limited use in surgery. It was first described by Oribasius (Bussemaker and Daremberg, 1861) who recommended it as a sling for broken arms (as in fig. 16). It is still used as a collar and cuff for this purpose today. Two quick ways of tying it are shown in fig. 17 and 18.

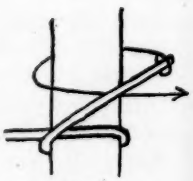

FIG. 18

ENDING A CONTINUOUS SUTURE

Ending a continuous suture is always a difficult problem. The majority of people use a reef, tying one strand in one hand against two in the other. This knot is bulky and unstable; furthermore, the adding of another half-knot does not increase its stability. There are two standard methods of

employing the reef in this situation. In the first (fig. 19, 20), the double strand is taken right through the final stitch, and tied against the free end which has not been pulled through. This is a more sensible way than the second method (fig. 21), in which the loose end is pulled right through, and tied against a bight drawn from the last suture. The reason for this latter method

FIG. 19

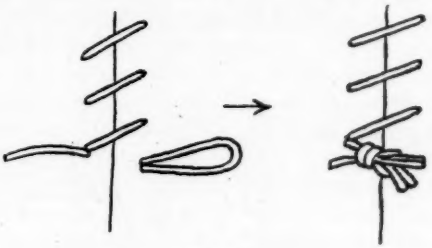

FIG. 20

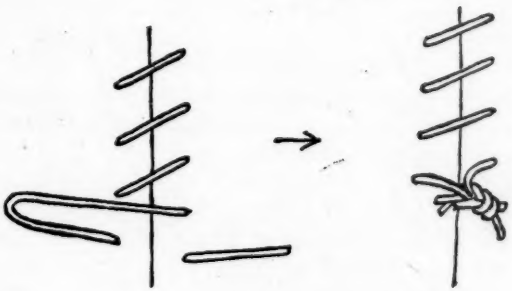

FIG. 21

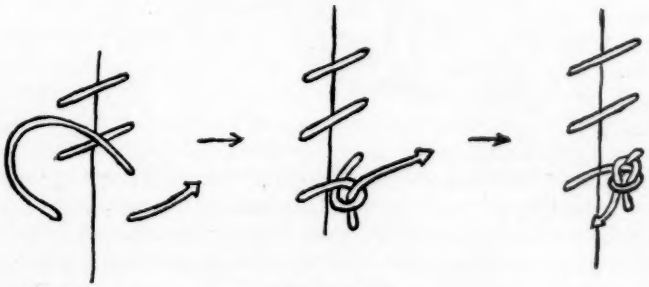

FIG. 22

being poor, is that the strain in the knot comes from three separate points, leading to easier disruption.

A good way of ending the continuous suture has been described by Carr (1957), in which the final knot is not a reef but a *bowline*. This latter knot is compact and far stronger than the reef. The technique of making it is

depicted in fig. 22; for a more detailed account the reader is referred to the original article.

THE CONSTRICTOR KNOT

The last knot discussed in this article has not been described in medical literature before, but it is extremely useful. It is called the ***constrictor knot***, and its invention is generally attributed to Ashley in 1944, although Drew pictured it in 1931. The knot (fig. 23) draws tight by a steady pull on the

FIG. 23

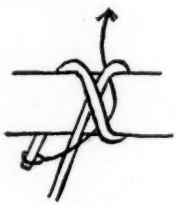

FIG. 24

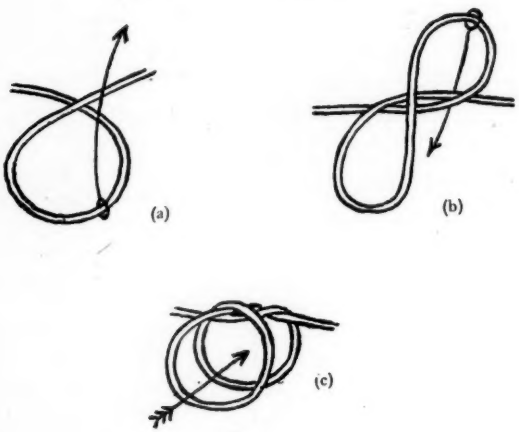

FIG. 25

two ends, and when drawn up has such a ratchet-like grip that it is impossible to loosen, and has to be cut apart. The greater the strain within the knot pushing outwards, the greater the grip. This is the criterion of a perfect ligature. It is an exceptional rarity for this knot to slip, and it is very easily tied, by either of two methods (fig. 24, 25).

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SOME MORAL AND ETHICAL ASPECTS OF MEDICAL HYPNOSIS

By AINSLIE MEARES, M.D., D.P.M.
Melbourne, Australia

THE early writers on Mesmerism and hypnotism devoted much space to vehement discussion of the moral, ethical and religious aspects of the subject. There were those who saw the trance state as the healing gift of God. Others saw it as a manifestation of the Devil, and many advocated that those who dabbled in such matters should be treated as sorcerers and witches. With the revival of the use of medical hypnosis since the 1939-45 War, however, there has been an almost complete absence of any serious discussion of this side of the subject. The present-day physician who would help his patients with hypnosis has no fear of being accused of sorcery; nevertheless, there is a number of moral and ethical aspects which invite open discussion, as they are likely to be overlooked when one first ventures into this field of medicine.

COMMON OBJECTIONS

There are first of all the commonly voiced objections to the use of hypnosis. For the most part these are the heritage of the religious criticisms of Mesmerism of the last century. With greater enlightenment, the opposition to hypnosis has changed ground from dogma and superstition to pseudo-scientific considerations. This category includes such matters as the domination of the patient, the weakening of the will, the possibility of immoral acts, the elicitation of secrets, the dangers of increased suggestibility, and the over-dependence of the patient on the therapist. It will be seen that, with ordinary precautions, these commonly raised objections are, in fact, invalid.

Before discussing these matters, let us assume that certain ethical prerequisites have been fulfilled. First, we assume that the matter of hypnosis has been explained to the patient, that he understands enough of it to be able to make a sensible decision, and that he desires treatment by hypnosis. Secondly, we assume that in the case of women patients and in the case of minors, the matter is discussed with some responsible relative or friend. Thirdly, we assume that there is no attempt to hypnotize the patient on the day on which he agrees to treatment by hypnosis. I regard this as quite important. It gives the patient a real opportunity to consider the proposition; so that there is no question of his giving ill-considered consent, and then being hurried into a procedure which he does not understand. This type of approach is necessary, as some suggestible persons can be hypnotized very easily, and even without their knowledge. I know this to be a fact, because it has inadvertently happened in my practice on two occasions.

Both patients were men. While I was testing their tendon reflexes, I gave a few suggestions of relaxation, and both fell into a hypnotic sleep. When they were awakened, both rationalized the situation in the same way, by saying that they had

not realized that they were so tired as to just fall asleep. An interesting feature was that neither patient knew I practised hypnosis.

Women and children are given the choice of having a third party in the room with them. They are simply asked: 'Do you think you can let yourself go more completely if nurse sits in here with you, or would you prefer her to stay where she is, in the office?' Some insecure persons gain a sense of security from the presence of a third person, and so can abandon themselves more easily in a passive induction of hypnosis. The purpose of the third party is to make the induction of hypnosis easier to the patient. The third party is not intended in any way as a protection for the patient: this, as in any other branch of medicine, lies in the physician's reputation.

A common criticism of medical hypnosis is that it is immoral to impose one's will upon another. This criticism implies that the patient is reduced to a mere automaton in the hands of the therapist. It would seem that this idea has arisen from observation of the behaviour of subjects during stage hypnosis. At one moment the victim eats a candle, next he plays an imaginary violin, then he is frantically swimming as he imagines he is being pursued by a shark. The point that is overlooked is that these antics of stage hypnosis are of no real psychological significance to the patient. If these victims of stage hypnosis were asked to do something psychologically significant—for instance, if a man were asked to hit his mother—the subject would no longer appear to be the same automaton, but would show his resistance in a number of defences. On the analogy of the behaviour of patients in hypno-analysis, it is likely that he would either suddenly fall into a deep hypnotic sleep, and so escape from the problem, or alternatively he would develop a pseudo-hysterical motor incoordination, so that when he went to hit his mother, he would in fact miss her. The idea that the hypnotist has a complete and utter mastery of the patient has no basis in fact. If it had, hypnotherapy would be a much simpler form of treatment than it actually is.

It used to be thought that there was the possibility of bringing the hypnotized patient to perform anti-social or immoral acts. There is a great deal of evidence which would show that if the ideas suggested are at variance with the subject's basic moral nature, the subject will react with anxiety, and the suggestions are not carried out. This means that a potential thief might be induced to steal under hypnosis, but not so an honest person. A woman of easy morals might be seduced, but not so a virtuous woman.

Another common criticism of hypnosis is that it is immoral to extract the patient's innermost secrets when he is not aware of the nature of the information which he is disclosing. In practice, in hypno-analysis, the matter is first explained to the patient along these lines. 'It may be that your condition is the result of conflicts deep in your mind. Hypnosis makes it easier for these ideas to be ventilated so that they can be worked out. They will then cease to disturb you'. The patient thus consents to the elicitation of ideas which may be merely suppressed on account of the hurt or humiliation which they cause him, or which may be completely beyond his consciousness.

A further criticism is that repeated hypnosis may increase the patient's suggestibility, so that at some time in the future he may be hypnotized by some unscrupulous person for anti-social or immoral purposes. The answer to this is simple. A patient who is easily hypnotized is given the post-hypnotic suggestion that he will never go into hypnosis unless he wishes to do so.

I was treating a married man in hypnotherapy. His main symptom was that he was too passive; he was never able to assert himself. He was easily hypnotized; so, in order to protect him from any future risk of being hypnotized against his will, he was given the suggestion that he would never go into hypnosis unless he wished to do so. The following two or three sessions were uneventful; then, on the next occasion, to my great surprise, I found that I was completely unable to hypnotize him.

It is often stated that treatment by hypnosis might induce an abnormal dependence of the patient upon the therapist. Of course, the sick always have some dependence on the physician who would help them. Beyond this, I have not noticed any abnormal dependent relationship of patients undergoing treatment by hypnosis. An unscrupulous physician in any branch of medicine can make patients dependent upon him if he wishes it; hypnosis would offer good opportunity to induce such dependence. It would be expected that any undue dependence of patients upon the physician would be reflected in the prompt payment of the physician's account for his professional services. It is an interesting commentary to the present discussion that in the author's practice, there is no significant difference in the payment of accounts by patients being treated by hypnosis, by waking psychotherapy, or by E.C.T.

MATTERS OF TECHNIQUE

These moral and ethical objections to medical hypnosis have been voiced so often that they are at least known to most physicians, but some matters of technique are less widely known and, as they are not generally understood, they may be open to unjust criticism from a moral or ethical standpoint.

One such matter of technique concerns touching the patient. Hypnosis is usually induced by offering the patient a series of graded suggestions. For the most part, these suggestions are given verbally. Suggestions, however, can also be given by non-verbal communications, by means of expression, gesture, attitude or general behaviour. Suggestions given in this fashion are often particularly effective, as there is less tendency for the patient to examine them critically. It is often possible to convey a powerful suggestion to the patient simply by touching him at just the right moment: a patient who is hovering on the brink of hypnosis will often become deeply hypnotized if he is gently touched on the forehead or the top of the head. The gesture has meaning to the patient, and works as a strong suggestion. This would seem simple enough. Nevertheless, touching one of our fellows is often a highly significant act. On the one hand, it may have a deep symbolic meaning and a profound psychological importance; on the other, it may be an incidental act of no consequence whatever. Because of this deeper meaning, we are careful in the way in which we touch our fellows. The physician would not ordinarily touch his patient in this way; but in hypnosis

it would seem wrong not to use a powerful symbolic mechanism, when it can so clearly be used for the benefit of the patient.

The technique of the direct stare is another procedure which might be criticized on ethical grounds. We ordinarily avoid staring into another person's eyes. Such an act is commonly associated with ideas of seduction or domination; and at a less clearly conscious level there are the ideas of the evil eye, and the eye of conscience. By virtue of this psychological aura, it can be used to convey powerful suggestion. The patient can be encouraged to look into your eyes and let himself go. He is told: 'You let your eyes look at me. It is easier to let yourself go. You look at me. You let yourself go. It is calm and easy and comfortable', and so on. In this technique there is no question of dominating the patient with a withering stare. Because of the symbolic mechanisms which are activated, it is much more effective than having the patient look at a bright object, as is commonly done in modifications of Braid's method.

In hypnotherapy there is necessarily an intense emotional relationship between patient and physician. This is hypnotic rapport. During the severe abreactions which are often a part of hypno-analysis, this emotional relationship of the patient with the therapist may become even more intense. Hypnotic rapport has been criticized as an unhealthy relationship. The validity or otherwise of such criticism would seem to depend upon the management of the situation. Hypnotic abreaction is itself a valuable therapeutic technique. The emotional relationship with the therapist can be effectively managed in either of two ways. The simplest method is to induce a complete amnesia for the session before waking the patient. Sometimes, however, it is desirable to allow the patient to remember what he wishes of the session, and to allow him to develop a spontaneous amnesia of any incidents which are too traumatic to tolerate in consciousness. In these circumstances, in the later part of the session the therapist withdraws emotionally from the patient by introducing a more and more matter-of-fact attitude into the suggestions. The patient is then put into a hypnotic sleep. This allows him to regain a complete emotional calm. The period between waking the patient and his departure is then used by the therapist to re-establish his relationship with the patient on a matter-of-fact basis.

There is another matter of technique which might well be brought to open ventilation as being a possible subject of criticism on ethical grounds. There is a large group of persons who go through life just holding off anxiety symptoms. They manage to keep going until some additional stress upsets their precarious equilibrium; then they break down: either with overt anxiety or with somatic equivalents. The precipitating stress is often some reality problem: housing difficulties, another pregnancy, an in-law coming to live in the house. The patient is usually tided over the difficult period by sedation, reassurance and emotional support by the general practitioner. Some patients, however, require rather more. These can often be helped through the difficult period by a few sessions of simple hypnotic suggestion.

The patient has often been trying very hard to battle through on his own. Often he has prayed to God for strength that he might overcome his difficulty. He gains strength from hypnosis. It seems a fulfilment of his prayer; and he comes to equate the treatment as some kind of religious experience. The patient does not express the idea in so many words, but my own experience would lead me to believe that this type of reaction is by no means uncommon. My own practice has been to maintain a complete passivity in the matter so that the patient interprets the experience in terms of his own psychological integration. The situation presents the obvious ethical problem. Is it right to allow the patient to interpret his treatment in this light? It is assumed, of course, that he does not attribute any abnormal powers to the therapist.

PERVERSE MOTIVATION

I now come to discuss a more difficult part of the subject. This consists of some matters which I consider are real moral and ethical hazards in the practice of medical hypnosis. These concern perverse motivation. A number of people seek treatment by hypnosis for relief of their symptoms. With full psychological examination, however, it becomes clear that it is not so much the relief of symptoms which has brought the patient to consultation, but rather a desire for the experience of hypnosis itself. This is always well rationalized, and the patient is never fully aware of the forces which bring him to seek treatment by hypnosis. Thus a masochistic woman who has psychoneurotic symptoms will seek treatment by hypnosis, not so much for the relief of her symptoms, but rather for the satisfaction of her yearning to be overpowered, which she expects to be fulfilled in the process of hypnosis. In a similar way, a woman of masculine-aggressive personality will often seek hypnosis for the opposite reason. She believes that she will not be hypnotized. By inviting a man to hypnotize her, she will prove to herself again that she will not submit to any man. Other patients of either sex often seek treatment by hypnosis because they feel the intensity of hypnotic rapport as an erotic relationship, either on a heterosexual or a homosexual basis, according to the sex of the patient. These matters are not just questions of theoretical academic interest; but are practical everyday problems of anyone who uses hypnosis to help his patients. The therapist has a clear obligation to protect such patients from their own perverse motivations.

Unfortunately, perverse motivation is by no means confined to the patient. Similar mechanisms operate to drive persons to practise hypnosis. Thus, the induction of hypnosis allows the therapist ample scope for the use of authority. It would seem beyond doubt that some therapists are perversely motivated, in that they use hypnosis not only to help the patient, but also that they themselves may gain satisfaction of their own unconscious desire to act with authority. In a similar way, hypnosis gives great opportunity for display; and I would think that many therapists who are anxious to display their hypnotic prowess by giving clinical demonstrations, are doing nothing more than finding an outlet for their own unconscious hysteroid drives.

Unconscious eroticism coming from the intensity of hypnotic rapport may also lead the physician to suggest treatment by hypnosis. This mechanism, of course, may function on a latent homosexual basis with male patients. Likewise, those therapists who habitually test the depth of hypnosis by sticking pins into the patient may well be driven to such a method by their own inner sadism. These are moral and ethical matters; and it would seem that everyone who practises hypnosis should not only explore the patient's real reason for seeking treatment, but should also learn enough of his own personality to be able to make some reasonable examination of his own motivation.

EXTRA-SENSORY PERCEPTION

There is one last matter concerning the ethics of medical hypnosis which I feel should be openly discussed. It concerns extra-sensory perception. This matter is so near what some describe as the 'lunatic fringe of psychiatry' that many present-day practitioners are chary of reporting cases for fear it might adversely affect their practices. However, in the past hundred years there have been published many accounts of telepathy and clairvoyance with deeply hypnotized persons. More recently, much controlled experimentation has been done on the subject. I myself simply do not know if extra-sensory perception occurs in hypnosis, or not. But on two occasions, incidents have occurred for which I can find no logical physical basis.

Some four or five years ago, I was treating a woman by means of hypno-analysis. I was using a technique which I have come to call hypnography, in which the deeply hypnotized patient projects his conflicts by painting with black paint. The hypnotized patient was seated at a table. I was seated behind her, writing down what she said about the things she painted. She had made two paintings. Then, in preparation for writing down her comments about the next painting, I wrote down the figure '3'. I was very surprised to see the patient also write down the figure 3, although nothing had been suggested to her. So I told her: 'Your hand will write down a number'. At the same time I wrote another number. To my surprise the patient wrote down the same number. She did this six or seven times, making only one mistake. At this stage, it occurred to me that the patient was paying me to cure her psychoneurosis not to have me experiment with her; so I discontinued the experiment in extra-sensory perception.

The other case was that of an Indian student who was being treated by the same technique. One day he asked me if I believed in telepathy. I told him that I did not know, and I invited him to experiment. Before he was hypnotized, it was arranged that I would ask him to write down a number, and at the same time I would write down a number myself. He scored a high percentage of successes. Next day, I had the hospital pathologist come to the session as a witness; but on this occasion there was no success at all.

If extra-sensory perception does occur in hypnosis, it must place a great moral responsibility on the therapist. He must be careful to control his thinking lest any negative thought about the patient might act as counter suggestion. For instance, if the therapist were to have the thought, 'This man will never get better', such a thought, without its expression in words, might have a harmful effect on the patient. As I have said, I do not know if extra-sensory perception occurs in these circumstances, or not; but it would seem to be an area which calls for urgent scientific investigation.

GENERAL PRACTITIONERS' FORUM

TRIAL OF A LIQUID ANTIPYRETIC IN PÆDIATRIC PRACTICE

By D. C. SAUNDERS, M.B., B.Ch., B.Sc., D.C.H.
Penygraig, Rhondda, South Wales

The following is an account of my clinical experience with a liquid form of N-acetyl-para-aminophenol ('elixir of febrilix'; N.A.P.A.) in infants and children to assess its value as an antipyretic agent, and also any analgesic effect it may have.

MODE OF ACTION

N.A.P.A. has been known since 1889 and the therapeutic effect is linked with that of acetanilid and phenacetin. It is thought that the antipyretic and analgesic actions of these drugs are due to the major portion being converted to N.A.P.A. in the body. The side-effects of acetanilid and phenacetin are not due to the formation of N.A.P.A. but to the formation of other metabolites from their remaining fractions.

The primary action of N.A.P.A. is believed to be a central one on the hypothalamus and thalamus. The drug is excreted mainly in the urine, either unchanged or conjugated with glucuronic acid. N.A.P.A. is said to have a low degree of toxicity and significant amounts of methæmoglobin are not produced. The compound is said to be non-irritating to the stomach.

SCOPE OF INVESTIGATION

The trial was carried out in an industrial type of general practice on infants and children. Fifty-three patients were involved in the clinical trial, and these included a typical selection of the febrile cases seen in general practice. Their ages ranged from under 1 year to 15 years. The vast majority (40) were in the age-group 2 to 8 years. There were 22 boys and 31 girls. It was impossible, except in one case, to take frequent daily temperature readings.

Method of administration.—The liquid preparation of N.A.P.A. was used in all cases. One or two of the older children were asked to try the liquid without dilution or masking and were able to swallow it, but all complained of its being bitter. All other patients were given N.A.P.A. in either orange juice, orange squash, lemonade, milk, 'ribena', or similar pleasantly flavoured vehicles. These solutions seemed to mask adequately the bitter taste and make the preparation quite acceptable to even the younger age-groups. The preparation is completely disguised in these liquids, whereas tablets, when crushed and dissolved, often have granules floating about which children are quick to observe and object to.

Dosage.—N.A.P.A. liquid was given in teaspoonful dosage, each teaspoon containing 120 mg. per 4 ml. The dosage scheme was as follows:—

Under one	2 ml. (60 mg.)	six-hourly
1-4	4 ml. (120 mg.)	,,
Over 4	8 ml. (240 mg.)	,,

RESULTS

The results are summarized in table I. The cases with a poor result were three cases of measles and one child with no definite diagnosis.

Assessment	Effect on temperature	No.	Per cent.
Good	Temperature normal, or near normal in 24 hours	39	73
Fair	Temperature normal on 3rd day	10	19
Poor	No response	4	8

TABLE I.—Results of use of N.A.P.A. in 53 febrile children.

Tonsillitis.—Eighteen of the patients were suffering from tonsillitis. Eight were given N.A.P.A. + an antibiotic, whilst 10 were given N.A.P.A. alone. The decision to use an antibiotic was made on the degree of severity of the systemic disturbance caused by the tonsillitis and not only on the appearance of the tonsils. As will be seen from table II, there appears to be no appreciable difference in the children treated with N.A.P.A. alone

N.A.P.A. + Antibiotic						N.A.P.A. only					
1st day		2nd day		3rd day		1st day		2nd day		3rd day	
F.	C.	F.	C.	F.	C.	F.	C.	F.	C.	F.	C.
100	37.8	99	37.2	98.4	36.9	100	37.8	98.4	36.9	98.4	36.9
100	37.8	99	37.2	98.4	36.9	101	38.3	98.2	36.8	98.4	36.9
102.5	39.2	98.4	36.9	98.4	36.9	100	37.8	99.8	37.6	98.4	36.9
*103	39.4	98.8	37.1	98.2	36.8	101	38.3	99	37.2	98.4	36.9
102	38.9	101.4	38.6	99.5	37.5	100	37.8	98.2	36.8	98.4	36.9
*101	38.3	98.6	37	98.2	36.8	100	37.8	98.4	36.9	98.2	36.8
103	39.4	98.2	36.8	98.4	36.8	101	38.3	98	36.7	98.4	36.9
102	38.9	99	37.2	98.4	36.8	102	38.9	98.2	36.8	98.2	36.8
						101	38.3	98.4	36.9	98.4	36.9
						100	37.8	98.2	36.8	98.4	36.9

TABLE II.—Comparison of effect on temperature of N.A.P.A. + antibiotic and of N.A.P.A. alone. Those cases marked * were noted by the parents to have a distinct fall in temperature about 1½ hours after N.A.P.A. was given.

and those treated with N.A.P.A. and an antibiotic. The antibiotic was oral penicillin V (phenoxymethylpenicillin) except in one case of penicillin sensitivity which was treated with sulphonamide. To date, there have been no complications such as nephritis, rheumatic fever, or erythema nodosum in either group.

The patients old enough to give sensible answers were asked if their throats felt less painful after N.A.P.A.; twelve said there was considerable relief from pain on the second day of treatment.

Measles.—Four patients suffering from measles were given N.A.P.A. Two of the patients were studied from the earliest prodromal phase of the

disease and N.A.P.A. was given immediately. The N.A.P.A. appeared to have no effect on the classical temperature curve of this disease: namely an initial rise, followed by a fall and then a further rise. The two other cases of measles were seen at the time of eruption of the rash and were given N.A.P.A. but the fall of temperature was in no way different from that in the two previous cases.

Dysentery.—During the trial there was an epidemic of dysentery in the area, the cause in the majority of cases being identified as Sonne or *Salmonella typhimurium* infection. The seven patients were treated with 'cremomycin' and N.A.P.A. Only two did not have a satisfactory fall of temperature after twenty-four hours and one of these vomited after each dose of N.A.P.A. which was discontinued after the third dose.

No definite diagnosis.—This type of diagnosis, although unsatisfactory, is unavoidable in a general practice. There were seven patients in this group with the presenting symptoms of malaise and on examination only an elevated temperature was found. There was a satisfactory fall in temperature within twenty-four hours in six patients and one patient showed a rise in temperature on the second day which eventually fell to normal on the fourth day.

Allergy and side-reactions.—No patient was observed to have any cyanosis. The drug was stopped in the following cases.

Case 19.—A girl, aged 4, suffering from dysentery. She vomited after each dose of N.A.P.A. including the third dose which was reduced to 4 ml. (120 mg.). The drug was then stopped. This patient was subsequently proved to have *Salmonella typhimurium* infection.

Case 44.—A boy, aged 6. He vomited after each dose of N.A.P.A. and the drug was stopped after three doses. This child has atopic eczema and asthma; these were not affected by the N.A.P.A.

Case 48.—A girl, aged 8. She had severe pharyngitis and some slight signs in her chest. She was given N.A.P.A. and 'chloromycetin palmitate suspension', 4 ml. four times daily. On the third day she developed a hæmorrhagic urticaria. All drugs were stopped and it was then found that a skin wound had been treated with 'chloromycetin ointment' three weeks previously. The condition responded to calamine and antihistamines, and two weeks later a test dose of N.A.P.A. was given and no untoward reaction occurred. It was assumed therefore that the eruption was due to chloramphenicol following sensitization by the skin ointment.

Parents' comments.—Many parents were impressed with the ease of administration so long as a suitable masking liquid was used and it did not necessitate the crushing of tablets. Two parents made definite observations that N.A.P.A. exerted its antipyretic effect within one to two hours of administration.

CONCLUSIONS

N-acetyl-para-aminophenol (N.A.P.A.) appears to be a stable liquid which keeps well under ordinary conditions.

It is easy to use and readily acceptable by patients of all ages if in a suitable masking liquid and it has no obvious smell when so disguised. Even when two large teaspoonsful of N.A.P.A. were given, only a slight taste was noted when orange squash was used.

N.A.P.A. has a definite antipyretic effect which, in my opinion, compares well with the routine drugs in use, such as soluble aspirin and its various varieties.

A definite analgesic effect was noted in tonsillitis and tonsillar neck-gland enlargement.

No serious toxic effects were noted and in only two cases was the drug found to be unsuitable as a result of vomiting which did appear to be due to N.A.P.A.; one of these was known to have a definite allergic diathesis.

It appears from these findings that N.A.P.A. is suitable for pædiatric practice and has the great advantage that it is a liquid preparation.

I wish to thank Dr. P. T. Main, of Boots Pure Drug Co. Ltd., for a generous supply of 'elixir of febrilix'.

HYPNOSIS AS AN ANÆSTHETIC AND ANALGESIC IN MIDWIFERY

By A. FRY, M.R.C.S., L.R.C.P., D.M.R.
*London, S.E.*25

Hypnotic anæsthesia or analgesia is one of the safest methods of conducting painless labour. According to DeLee and Greenhill (1939), 'the only anæsthetic that is without danger is hypnosis. Psychiatrists claim that no person ever died under pure hypnosis. I have used suggestion a great deal, indeed almost constantly, and I am irked when I see how my colleagues neglect to avail themselves of this harmless and potent remedy'.

I therefore decided to investigate the possibilities of using hypnosis in my obstetric practice.

SCOPE OF INVESTIGATION

Hypnosis was used in 20 cases in general practice: 16 were delivered at home and four in nursing homes. In all of them full anæsthetic and analgesic effects were obtained without the use of drugs or inhalation anæsthesia, except in one case of a very neurotic mother, who had to be given 20 minims (1.3 ml.) of trichlorethylene for forceps delivery.

The training of the expectant mothers was carried out during the routine antenatal visits, which involved an extra twenty to thirty minutes each time. The number of the hypnotic sessions varied from four to eight per case. As expectant mothers are usually good hypnotic subjects, there was a good response in all the cases. The main objects of the training were complete physical and mental relaxation, the elimination of fear and apprehension related to labour, and hypnotic perineal anæsthesia through post-hypnotic suggestion. The midwives and nurses, as well as the expectant mother's relatives who were likely to be present and assist in the labour and who were

willing to cooperate, were given detailed instructions about their attitude so as not to interfere with the hypnotic process.

RESULTS

The average duration of the first stage of labour in the 12 primiparæ was 6½ hours, and of the second stage 1¼ hours. In the eight multiparæ these were 2¼ hours and ½ hour respectively.

There were no complications following the deliveries. The third stage of labour was very short and post-partum blood loss was very slight. All the mothers felt very well after parturition and there was not the slightest feeling of fatigue. So successful was the relaxation, including that of the perineum, that seven multiparæ had no perineal tears during their deliveries including one case in which the infant weighed 9 pounds 6 ounces (4.25 kg.). The eighth multipara had an intact perineum after her previous delivery and it remained so following the delivery under hypnotic anæsthesia.

The strong rapport which was established with the mothers during the hypnotic training was very helpful in the postnatal period. Advice and guidance given to them about the management of the baby and of themselves were more strictly adhered to and followed, than in the case of the mothers who were not delivered under hypnotic anæsthesia. This was well illustrated in breast feeding, which was successfully established in 17 mothers out of the 20: a much higher percentage than is generally reported nowadays.

There were four forceps deliveries, one extended breech and three episiotomies performed under hypnotic anæsthesia and analgesia.

ILLUSTRATIVE CASES

Case 1.—Para–3, aged 30. In her first labour the first stage lasted eight hours, the second stage 1½ hours, and a ruptured perineum had to be repaired with seven sutures. In her second labour the first stage lasted six hours, the second stage one hour, and the perineum was ruptured again and was repaired with five sutures. Gas and air analgesia and pethidine were used on both occasions. The weights of the infants were 7 pounds (3.18 kg.) and 7 pounds 4 ounces (3.29 kg.) respectively. In her third labour she was successfully trained under hypnosis during five sessions in the last two months of her pregnancy. She started labour at full term—at 11.00 hours. The uterine contractions were slight and completely painless. When she was seen at 17.00 hours the cervix was fully dilated, but there was no realization by the mother that labour was imminent as the whole first stage was painless, although uterine contractions were felt. An infant weighing 7 pounds 4 ounces (3.29 kg.) was born at 17.10 hours without the slightest discomfort or pain. The perineum remained intact. The blood loss was so slight that there was no need for ergometrine. The patient commented on how much better and fresher she felt this time than she did after the two previous deliveries.

Case 2.—Primipara, aged 28. She was trained in six sessions which were so successful that she was able to self-induce a fairly deep hypnotic state. She started labour on the expected date with rupture of the membranes at 10.00 hours, but there were no uterine contractions until 16.00 hours. When they started later, they were slight in the beginning, but as they got stronger, about 18.30 hours, she began to relax and felt no pain, until after the delivery at 20.30 hours, which was uneventful. Only the midwife was present, who remarked how well relaxed and free from pain the mother was, regardless of the fact that no pethidine or gas and air analgesia was used. The infant weighed 7 pounds 12 ounces (3.5 kg.). The perineum was intact.

This case illustrates well that it is possible to train an expectant mother to reach

by herself a relaxed state during labour, free from fear and pain, even without the presence of the training doctor during labour and without the enforcement by him of the hypnotic state during the second stage of labour.

Case 3.—Para–3, aged 27. The first infant, weighing 8 pounds (3.47 kg.), was born in hospital. It was a forceps delivery with a ruptured perineum. The second infant, weighing 8 pounds 8 ounces (3.7 kg.) was delivered normally, but the perineum had to be repaired again. Hypnotic training was carried out in six sessions during the last four months of the third pregnancy. The labour was ten days overdue, when it started with slight uterine contractions. The first stage was completed in 2½ hours; the contractions were painless and the mother was well relaxed. An infant was born weighing 9 pounds 6 ounces (4 kg.) nearly 20 minutes later under successful hypnotic anæsthesia. The perineum was so well relaxed that it remained intact, and needed no surgical attention. When the mother was asked after the delivery how she felt, she said that she would not mind having another six babies under similar conditions and in the same way.

Case 4.—Primipara, aged 20. She was trained in eight antenatal hypnotic sessions, and was able to reach a fairly deep hypnotic state and to achieve perineal anæsthesia. The labour, about full term, started at 10.00 hours with slight uterine contractions. The first stage was completed at 15.30 hours. The mother was comfortable and the contractions painless. There was no advance after 17.00 hours. Although the contractions were very strong, signs of fœtal distress became apparent. It was thought that the delay might be due to a short cord. The mother was then prepared for forceps delivery. Hypnosis was induced and suggestions were given that she would be comfortable, free from any pain, conscious when the baby was born and that the only sensation which she would have would be a feeling of pressure on the perineum, which would remain anæsthetic, and an infant weighing 7 pounds 4 ounces (3.29 kg.) was delivered with a tight convolution of the cord round the neck. The perineum remained intact. The mother was conscious during the delivery, but the hypnotic anæsthesia of the perineum was so perfect that she thought that the forceps, when she saw them, were lying on the bed, when actually they were inside the vagina. The delivery was completely painless. The mother felt fine and fresh, and her first remark after the birth of the baby was: 'I feel starving and I could eat a horse'.

Case 5.—Primipara, aged 28. She was trained in six sessions during the last four antenatal months. The first stage lasted eight hours. The contractions were painless and not very frequent. After about 1½ hours in the second stage, the perineum began to show signs of splitting. This was before the head of the baby was showing and was due to considerable scarring of the perineal tissue, a result of several abscesses in that region many years ago. In order to prevent a complete perineal tear it was thought advisable to perform an episiotomy. This, the delivery and the repair were all performed under successful hypnotic anæsthesia. When the mother was brought out of the hypnotic state she stated that she did not feel any pain or discomfort whatsoever. The infant weighed 6 pounds 4 ounces (2.72 kg.).

Case 6.—Primipara, aged 28. She was trained in six sessions. Labour started at 01.00 hours, three weeks before the expected date. The first stage was seven hours and the uterine contractions were painless. The second stage lasted one hour. The presentation was an extended breech. The hypnotic state was deepened, episiotomy performed and the infant delivered without great difficulty. The mother felt no discomfort or pain during the delivery and even the suturing of the episiotomy was completely painless. The weight of the infant was 4 pounds 12 ounces (2.15 kg.).

Case 7.—Primipara, aged 35. She was trained in eight sessions. She went to full term and the first stage lasted ten hours. She was well relaxed and the uterine contractions were not unduly painful. There was no advance after two hours in the second stage. A deeper hypnotic state was induced, forceps were applied and an episiotomy performed. A 7-pound (3.18 kg.) infant was delivered with a short cord convolution round his neck. The hypnotic anæsthesia was very successful.

Case 8.—Primipara, aged 20. The patient was very tense, and there was a history of nightmares in childhood, sleepwalking and strong phobic reactions, for which she was treated in hospital. The patient's mother was also a very neurotic type. The

expectant mother was trained in seven sessions, and after some initial difficulties was able to relax satisfactorily. The labour was one week overdue. The first stage lasted eight hours and she was relaxing well. After about 1½ hours of the second stage there was very little advance, although the uterine contractions were very strong. When signs of fœtal distress appeared it was decided to apply forceps. Deeper hypnosis was induced, but the patient panicked due to interference by her neurotic mother and the anæsthesia was only partly successful. As a result, 20 minims (1.3 ml.) of trichlorethylene on an open mask had to be administered when the forceps were applied. An 8-pound (3.47 kg.) infant was delivered with tight cord convolutions round the neck and foot. The perineum was repaired with one suture and this was painless. The third stage was normal.

DISCUSSION

For untold ages women have looked upon the birth of a child as an ordeal of pain and suffering. As a result, they approach it with fear and apprehension. The challenge of this situation lies in the fact that a normal spontaneous childbirth is a natural physiological process. Why then should there be pain connected with it? The best answer to this question is that we are dealing with a psychological problem. So many mothers, from childhood onwards, have heard about the birth pains and the dangers of childbirth that, acting under these suggestions and this type of conditioning, they go into labour with fear and apprehension, expecting pain, with the result that the contractions of the uterus which give unaccustomed sensations immediately produce muscular tension inhibiting the normal process of birth. The difficulties of childbirth are largely the result of mental hazards, and our problem is to reduce and eliminate these hazards. The use of drugs for the relief of pain and so to influence the patient's mental condition is treating the symptoms rather than eliminating the cause of these symptoms. There is no known drug used for this purpose at present without some element of danger in its use, either to the mother or to the baby or to both.

It is not the work involved in childbirth which we can hope to eliminate, nor is it the discomfort associated with that hard work. It is the pain and mental anguish of childbirth which are completely unnecessary and which can be eliminated in the normal, healthy and intelligent woman. To exchange one or two hours spent in pleasant, comfortable antenatal training for some of the hours spent in the first stage of labour is a bargain which most women will be glad to make.

Hypnotic anæsthesia and analgesia are perfectly safe in the conduct of obstetric cases in general practice. No special pre-anæsthetic preparation of the patients is necessary when faced with obstetric emergencies. The advantages and disadvantages of the uses of hypnosis in labour have been admirably summed up by Schneck (1953):—

Advantages:—

(1) Hypnosis is not a complicated procedure. Any physician can be taught this method.

(2) No apparatus or expense is involved.

(3) There is no respiratory or circulatory depression in the mother or fœtus.

(4) Hypnosis raises the resistance to obstetric shock, circulatory and respiratory failure. Drugs act in the opposite way.

(5) Resistance to fatigue is definitely raised during hypnosis. Hence there is little or no maternal exhaustion which is undoubtedly a contributory factor in the production of sepsis and shock.

(6) There is complete dissociation instead of hyperexcitability. Patients are calm, quiet and relaxed.

(7) Hypnotic anæsthesia and analgesia are easily controlled.

(8) The pain threshold is effectively raised under hypnosis by the removal of fear and tension.

(9) The blood loss is decreased during the hypnotic state.

(10) The undivided attention of the physician is not always required if trained personnel are available. Rapport can be transferred to somebody else. But it is desirable for better success if the physician is present for at least part of the time during the termination of the second stage.

(11) There is no increase in the incidence of operative delivery but, if necessary, certain operative procedures, such as application of forceps or suturing of the perineum, can be painlessly carried out.

(12) Complete relaxation or contraction of the abdominal wall and perineum can be produced simply by command.

Some disadvantages:—

(1) Due to erroneous misconceptions, the lay person feels that there is a stigma attached to being hypnotized.

(2) Time and effort are required to give the antenatal hypnotic training, but this does not represent such a great difficulty. The monthly visits for the routine check-up are used for the rehearsal of trances, education and elimination of fear. This should not take more than fifteen to twenty minutes.

(3) All people are not susceptible to hypnosis, which is a highly individual problem since it varies from patient to patient but, on the whole, expectant mothers are more easily hypnotized than ordinary women. Some degree of suggestion is achieved in about 90 per cent. of cases and deep hypnosis in 25 per cent.

All these points have been proved by the experience gained from the conduct of the cases which I have conducted and hypnotic anæsthesia or analgesia is one of the safest methods of conducting a painless labour.

SUMMARY

Details are given of 20 confinements in which anæsthesia or analgesia was successfully induced by hypnosis.

These results confirm the experience of others that hypnosis is a safe and effective method of inducing anæsthesia or analgesia in obstetric practice.

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A CASE OF CHRONIC SUBDURAL HÆMATOMA

By J. G. COONEY, M.B., B.Ch.
Sheffield

According to Cecil and Loeb's 'Textbook of Medicine' (9th edition), the incidence of subdural hæmatoma following head injury is variously estimated at 1 to 10 per cent., depending upon the severity of the injury. Because of the greater incidence of head injury in males, it occurs predominantly in men. According to whether the symptoms develop at the time of the injury, or appear after an interval of several weeks or months, it is classified as acute or chronic. In some of the latter cases the previous head injury may have been so slight as to be forgotten. There are no characteristic symptoms which will seem to differentiate a chronic subdural hæmatoma from an intercranial neoplasm.

I append a description of a case of a chronic subdural hæmatoma which occurred in my practice several years ago.

CASE RECORD

The patient was a man, aged 66 years, who complained of intermittent headaches, and vertiginous attacks over a period of eight weeks, followed by loss of use in the left arm and the left leg, the latter being a more recent development. The immediate past history was interesting. He told me that he had been employed as a pointsman in the local transport department, and in the course of his duties he had been knocked down three months previously by a motor car and sustained an injury to his head, which necessitated the insertion of three stitches in the right temporal region.

Examination.—He was a small thin man. There was no evidence of stupor or coma, and his speech was unaffected. There was a scar, approximately 3 inches (7.5 cm.) long, in the temporal region. The most striking sign was a partial loss of use in the left arm and the left leg, which showed a positive Babinski. In view of the previous head injury and the development of the left hemiparesis, a diagnosis of chronic subdural hæmatoma was made.

He was admitted to the neurological unit at the Royal Infirmary, Sheffield, where the diagnosis was confirmed by operation. Unfortunately pneumonia developed and he died shortly afterwards. As there was a definite connexion between the cause of death and the original head injury, the matter was reported to the coroner.

The *post-mortem examination* disclosed that the injury which he had received when knocked down by the car had resulted in a rupture of the vessels of the right meningeal artery, giving rise to bleeding in the right subdural space. There was a mass of subdural clot covering the parietal region. The clot was old and had undergone partial organization, and was separated by a membrane from the surface of the brain.

As a result of the post-mortem examination, the widow of the patient applied for compensation, and was awarded the sum of £500.

CURRENT THERAPEUTICS

CXLI.—COUGH SUPPRESSANTS

By J. D. P. GRAHAM, M.D., F.R.C.P.Ed., F.R.F.P.S.

Senior Lecturer in Pharmacology, Welsh National School of Medicine

THE vast number of 'cough cures' available is a reflection of the frequency with which this symptom gives trouble and of the lack of effective means for controlling it. During the last decade efforts have been made to understand the physiology and pathology of coughing and associated phenomena such as the calibre of the bronchi and the state of the bronchial secretion and to develop specific agents for correcting abnormalities. Before the value of these efforts can be assessed, it is desirable to have a clear understanding of the process which the medicaments are intended to modify.

THE NATURE AND ORIGIN OF COUGHING

Coughing, both the hollow sound and the expulsive effect, results from increased velocity of expired air. Normally, expiration is a passive act resulting from elastic recoil of the previously inflated lung and thorax and even during hurried breathing this is so. But during the act of coughing active participation of the expiratory muscles plays a large additional part. Since it is difficult to make an effective forcible expiration unless the chest is distended the inspiration which follows the effective stimulus and which precedes the expiratory cough is of prime importance to the result. The truth of this is manifest during whooping-cough. A greatly increased inspiration produces a strong Hering-Breuer reflex and thus starts off the following expiration explosively. In addition one observes a closure of the glottis at the beginning of the expiratory phase of cough which reinforces the effect by narrowing the air blast and allowing time for coordination of the muscles involved. But cough occurs perfectly well after tracheotomy. Bronchospasm always accompanies the expiratory phase. All this activity, though it may be initiated voluntarily, is usually a repetitive spasmodic reflex. Almost any sort of stimulus may initiate the reflex so that there cannot be specific 'cough' nerve-endings but mechanical stimuli are particularly effective at the bifurcation of the trachea, and chemical stimuli from inhaled irritants or noxious secretions on the mucosa of the trachea. Adaptation to the former occurs after a time but not readily to the latter, at least under experimental conditions. Many other areas than these give rise to 'false cough' because the abnormal stimuli activate the same afferent paths and the reflex pattern of coughing is so clearly defined that no matter what the stimulus the result is a 'cough'. Thus, irritation of the stomach, dry pleurisy, pneumonitis, pressure on the trachea, are well-known causes of cough.

There is no precise 'cough centre' in the medulla, and connexions with higher centres are much used to initiate, encourage or suppress coughing.

THE STATE OF THE BRONCHIAL SECRETION

Since the commonest stimulus for coughing is irritation of the mucosa, the state of the bronchial secretion is closely related to it. This secretion is normally caused to flow towards the glottis by ciliary action. The activity of the cilia and hence the question of whether or not mucus is moved has been shown to be related to local cholinergic activity which may be increased by eserine or abolished by atropine. The copiousness and viscosity of the secretion is controlled by parasympathetic secretory nerves, so that reflex stimulants of these (*expectorants*) soften the mucus and render it less irritant. It is improbable that those expectorants which work by irritating the stomach can be very effective in doses which avoid the nauseating results of gastric disturbance but potassium iodide which seems to act directly on the mucous cells may be an exception. Sputum may be purulent when there is an open breach of the lung or mucosa, muco-purulent when there is pus and increased secretion, or purely secretory. The purulent element will only disappear when the wound is healed and expectorants and cough suppressants will not do that. That which proves obstructive can be removed by postural drainage or voluntary bouts of coughing. The secretory element is seldom troublesome if copious but in chronic bronchitis and asthma may be tough and extremely irritating. Mucolytic or softening agents may thus be of value. Finally, one must remember that coughing is a protective reflex since it may expel harmful matter but that most sputum is swallowed. The rise in intrathoracic pressure during coughing is extreme and the strain on the heart and vessels consequently great. Subconjunctival hæmorrhage in whooping-cough is a reminder of this. Bronchospasm permits the act of coughing to extend back into the lung but, if combined with the presence of tenacious mucus, may precipitate failure of aeration, as is seen in asthma. This precludes effective coughing and starts a vicious circle.

It follows that the reflex arc may be interrupted at a number of places, and agents to do so, both old and new, are legion. I make no distinction between suppressants and expectorants, which merely approach the same goal by two ways.

EVALUATION OF ANTITUSSIVES

This is not as simple a matter as might at first appear because the relation between efficacy in suppressing cough induced artificially in animals and suppression of cough in patients is not clear. The tests may be carried out on animals or in man. The former may be anæsthetized (which facilitates technicalities but obscures results) or unanæsthetized. The stimulus may be mechanical (such as passing a feather or a plastic tube down the trachea) or chemical (e.g. dust, weak acid or alkali) and the animals used are often cats, dogs, rabbits or guinea-pigs. Also, one may stimulate the recurrent

laryngeal nerves by direct application of electrodes or by remote control of implanted electrodes. Drugs are injected by various routes and comparisons made of the incidence, number, duration and type of coughs and the effect of the drugs upon them. Various assay procedures as to dosage scales, alternation of drugs, cross-over tests and the like are employed to help evaluate the results. The toxic or even lethal doses can also be found and a rough therapeutic index derived.

In healthy volunteers the usual procedure is to inhale an irritant aerosol and to test various drugs and doses by repetition at intervals in the same persons, using a 'blind' technique so that as little subjective bias as possible creeps in. These precautions, and the inclusion of placebos, become more essential as the agent is tried out on patients. Clearly defined criteria for inclusion of individuals in the trial and for recording of effects are of equal importance with random selection and control of bias in the recorders in this sort of work. In few cases have such rigid tests been applied to cough medicines but the situation improves as new medicaments seek for a place in this crowded field. The method of sequential analysis is of particular value since it enables a valid answer to a simple question to be provided quickly, and there are so many drugs to be investigated.

The desired interruption of the reflex may be attempted at one or several of the following points:—

(1) The trigger area.
(2) The afferent side.
(3) The efferent side.
(4) The central regions.

A combined attack on the problem is usual.

THE TRIGGER AREA

(1) *When the underlying pathology is relieved*, e.g. by surgery, chemotherapy or the passage of time, the precipitating cause of the coughing should be gone and, unless the reflex has become much facilitated, coughing should cease. Adaptation to the stimulus helps.

(2) *Local anæsthesia of the sensory receptor* includes:—

(a) *Inhalations of steams containing volatile matter having a local action:* e.g. benzoin inhalation, menthol and benzoin inhalation, menthol and eucalyptus inhalation, or menthol inhalation, all from the *British National Formulary* of 1957. A part of the effect is due to softening of tenacious mucus by the water.

(b) *Inhalation of conventional local anæsthetics:* e.g. cocaine hydrochloride as a spray. The use of this technique is confined to special cases.

(c) *Systemic local anæsthetics.* Recently the idea of giving substances by mouth which, after absorption, will preferentially reduce the sensitivity of pulmonary stretch receptors which initiate the Hering-Breuer reflex or the sensitivity of other afferent endings subserving cough reflex has been tried. Tertiary butyl naphthalene ('becantyl' [Horlicks]) is perhaps the most

effective. The idea is certainly novel and, as such, welcome, although it is too early to get enthusiastic about it. Another such is nonæthyleneglycol butylaminobenzoate ('tessalon' [CIBA]).

(d) *Creosote* is an old remedy in bronchitis: e.g. 'creolix' (Rybar), 'meditus' (Savory & Moore), used partly as an expectorant from its gastric irritative reflex, partly as a deodorant, but there is thought to be an element of anæsthetic action on the tracheal mucosa. This approach has been revived with the introduction of guaiacol glyceryl ether: e.g. 'distolyt' (Distillers Co.), 'pectabalm' (Crookes), 'pulmodrine' (Medo), 'respenyl' (Crookes), and 'robitussin (Robins), though their efficacy is doubtful.

(e) *Demulcents* such as liquorice lozenges B.N.F., and a host of elegant proprietary lozenges which help to soothe a dry or inflamed throat. So pleasant to take are some of these that children were happy to suck them when sweets were rationed.

(3) *Loosening, increasing, diminishing or otherwise trying to get rid of the irritating secretions.*

(a) *Mucolytic preparations* designed to soften tacky mucus and so permit of its being shifted. The attack is a direct 'in vitro' one, which serves to distinguish them from the better known expectorants. Steam from inhalants and water in aerosols are probably the most active constituents, but a detergent, e.g. 'alevaire' (Bayer), may be added. These substances tend to foam distressingly and, as there is no oil in sputum, have less effect on the interface tension than in the case of the grease they were designed to loosen. Tryptic enzymes, e.g. chymotrypsin from pancreas as 'lomudase' (Benger) is much advocated but there is little protein in mucus on which the enzyme can act. The expectorant effect is probably due to the results of irritation causing violent coughing and to water acting as a softener.

(b) *Expectorants*, classically, act by increasing the watery and alkaline constituents of secretion, thus loosening mucus. The soft, copious sputum may then be coughed up. The greater number of them are gastric irritants: e.g. ipecacuanha, ammonium chloride or carbonate, tartar emetic, senega, tolu or squill, probably citrates and the volatile oils. The latter may exert some local anæsthetic action. The number of such preparations is very great and the mixtures often contain substances which act centrally as well. They may perhaps be considered under three headings. I disclaim any suggestion that these lists are complete.

Under the first heading come preparations listed in the B.N.F. 1957 as facilitating expectoration:—

Ammonia and ipecacuanha mixture
Ammonia and senega mixture
Ipecacuanha and alkali mixture
Potassium iodide and ammonia mixture
Saline mixture
Ipecacuanha
Ipecacuanha and ammonia mixture for infants
Ipecacuanha and squill linctus for infants
Simple linctus for infants
Tolu compound linctus for infants
Sodium chloride compound mixture

Secondly are proprietary mixtures in which the main ingredient appears to me to be in this class and which are designated as 'ethical' because of restricted advertising and distribution by the manufacturers:—

'Children's C.M.' (Rybar)
'Cosylan' (Parke, Davis)
'Ipecopan' (Sandoz)
'Pectex' (Duncan Flockhart)
'Silbe C. Syrup' (Silten)
'Thoracin' (Hamol)
'Thymomellis' (Hewlett)
'Thymotussin' (Oppenheimer)

This list was compiled from *The Extra Pharmacopœia* and advertisements in the medical press.

Thirdly come the great number of 'non-ethical' cough mixtures on unrestricted sale to the public, most of which contain elements in several classes. I name only a few of the better-known ones, a list compiled from information from wholesalers: Owbridge's lung tonic, Venos cough cure, Zubes cough mixture, Galloway's mixture, glycerin, lemon, honey and squill.

Further, an expectorant action might result from drugs acting on the central part of this secretory reflex, e.g. apomorphine hydrochloride; on the efferent nerve ending or near it, e.g. choline esters and pilocarpine nitrate; or purely on the mucus cell, e.g. potassium iodide, and probably the volatile oils which have a complex action.

(c) *Drugs which dry up secretion*, usually atropine-like. They also suppress ciliary activity. Certain combinations of expectorants with drugs of this class are incomprehensible to the pharmacologist but are not the less popular for that. One may offer belladonna and ipecacuanha mixture for infants B.N.F. Of the proprietary preparations containing atropine, 'brovon' (Savory & Moore) also contains codeine and ephedrine.

THE AFFERENT SIDE

This part of the reflex arc can be interrupted by (a) ganglion blockers or (b) vagal block by infiltration of local anæsthetics. Fortunately, this side of the matter remains academic.

THE EFFERENT SIDE

Under this vague heading I propose to include such theoretical considerations as neuromuscular block (no properly curarized patient can cough, as the anæsthetist knows), and such practical matters as dilators of the bronchi. These may either inhibit parasympathetic nerve action which is spasmogenic, e.g. atropine, hyoscine, or imitate or stimulate the dilator sympathetics, e.g. ephedrine and isoprenaline, or act more directly on the muscle cells, e.g. nitrite, papaverine, theophylline. Many antihistamines have a degree of atropine activity. The B.N.F. offers a choice from 17 such preparations listed under the heading of 'preparations relaxing bronchial spasm'. It would be tedious to repeat a list so readily available but it may

be helpful to mention a few popular proprietaries in which a main ingredient appears to me to come under this heading:—

'Asmac' (Wander)
'Brovon inhalant' (Savory & Moore)
'Calcidrine' (Abbott)
'Ephretuss' (Evans Medical Ltd.)
'Franol' (Bayer)
'Ipesandrine' (Sandoz)
'Phedros' (Merck)
'Phensedyl' (May & Baker)
'Thymephrine' (Oppenheimer)
'Zephrol' (May & Baker)

Such preparations are perhaps of most value where cough is associated with asthma. Ephedrine is the usual ingredient.

THE CENTRAL REGIONS

Drugs which depress the coordinating regions can depress cough due to any type of stimulus. The appeal is obvious and the response has been eager. One may divide them into:—

(1) ***Opium, its extractives, derivatives and synthetic imitations.***

(a) ***Opium.***—This is not very popular but we find in the B.N.F. camphorated opium compound and the opiate linctuses of squill, and in *The Extra Pharmacopœia* opiate pastilles of squill in addition. Opium is uncommon in proprietaries.

(b) ***Morphine*** is more favoured: e.g. ammonium chloride and morphine mixture; ipecacuanha and morphine mixture B.N.F.; Linctus Morphin.; Linctus Morphin. Co.; Linctus Morphin. Rub.; Mist. Tussi Hydrocyan. (Brompton mixture), Mist. Tussi Rub., and Joll's Linctus of *The Extra Pharmacopœia*. 'Tussi-Rube' (Hewlett) is a proprietary preparation.

(c) ***Ethylmorphine*** is alleged to have less side-effects. Elixir ethylmorphine and terpin is non-proprietary, whereas Syr. Tussi HBr. (Harris), 'tancolin' (Maw), and 'tussibrom' (Richter) are.

(d) ***Diamorphine (heroin)*** is still used despite the frowns of WHO. Elixir Diamorphin. et Pini Co., Elixir of Diamorphine and Terpin, Glycerin of Diamorphine and Linctus of Diamorphine are in *The Extra Pharmacopœ.a*, and 'pinheroin' (Oppenheimer), 'elixir terp-heroin' (Woolley) and 'terpoin' (Hoseason) are proprietaries.

(e) ***Dextromethorphan.***—This derivative is used in 'romilar' (Roche).

(f) ***Morphinylethylmorphine***, or ***pholcodine***, is at present very popular. It is alleged to be very specific. It may be exhibited as pholcodine linctus B.N.F., syrup of pholcodine citrate or as any one of 20 or so proprietary preparations:

'Codinyl' (Hatrick)
'Codylin' (Ferris)
'Collobell (Bell)
'Copholco' (Wade)
'Copholcoids' (Wade)
'Elixir 231' (Mawdsley)
'Ethnine' (Allen & Hanburys)
'Folcovin' (Rybar)
'Glycodine' (Duncan Flockhart)
'Hewfolco' (Hewlett)
'Infantussin' (Hoseason)
'Lipect C.E.' (Wyeth)
'Memine' (Macfarlan)
'Phalcin' (Harris)
'Pholcodine syrup' (Duncan Flockhart)
'Pholcomed' (Medo)
'Pholtussa' (Harris)
'Rubelix' (Fletcher)
'Tusseprin' (Woolley)

(g) *Codeine* is still favoured by many despite its manifest drawbacks. Linctus of codeine B.N.F. is available and four other non-proprietaries in *The Extra Pharmacopœia*, as well as 'bromcodeine' (Crookes), 'bronchial lozenges' (Parke, Davis), 'elixir terpin and codeine' (Woolley), 'hicoseen' (Hommel), 'histadyl E.C.' (Eli Lilly), 'mulsivin' (Rybar), 'pavacol syrup' (Ward Blenkinsop), 'pulmolactis' (Clay), 'sedamyn syrup' (Merck); in addition a large number of 'non-ethicals' contain codeine.

(h) *Dihydrocodeinone* as 'dicodid' (Knoll), 'tussionex' (in the latter adsorbed to ion exchange resins to delay release) is similar.

(i) *Methadone*, a synthetic, is available as linctus of methadone B.N.F., or 'elixir methadone' (Smith), 'physeptone linctus' (B.W. & Co.).

(j) *Other alkaloids of opium*, such as 'narcotine-coscopin' (Evans Medical Ltd.), 'nicolane' (Nicholas), or cephaelin-sedatussin' (Eli Lilly), have been brought in.

(k) *Diethylpiperidine.*—'Sedulon syrup' (Roche) is a synthetic relative of pethidine.

(l) *Oxeladin* ('pectamol' and 'tussimol' [B.D.H.]) and *carbetapentane citrate* ('tocease' [Pfizer]) are in the category of synthetic relatives of morphine, stated to be devoid of toxic side-effects.

(2) *Antihistamines with a central depressant effect.* Most antihistamines, such as diphenhydramine, have a sedative action and lack the addictive, constipating and nauseating actions of opium alkaloids, but they are powerfully hypnotic. Curiously enough, none of them appears in the B.N.F., but there is a number of proprietary mixtures: e.g. 'benylin expectorant' (Parke, Davis), which contains diphenhydramine; 'orthoxicol' (Upjohn) with methoxyphenamine; 'piriex' (Allen & Hanburys) with chlorpheniramine, and 'thorpax' (I.C.I.) with phenothiazine.

(3) A number of *sedatives which show some activity in parkinsonism:* e.g. 'taoryl' (Geigy), containing caramiphen. It is improbable that effective doses can be free of side-effects.

CONCLUSIONS

There is a great demand for cough mixtures, and doctors and manufacturers have hastened to satisfy it. It is probable that most patients with acute cough do not need a suppressant; if they insist they should be told to buy some simple harmless linctus. No central sedative is harmless in effective doses, all having side-effects. If such is really necessary, a price has to be paid in gastro-intestinal upset and depression. At the moment, pholcodine is most favoured, though the antihistamines have their partisans. The most hopeful feature is the arousal of interest among the great pharmaceutical houses in possible new approaches. At last it is being realized that, since the public will continue to consume these things, they might as well have an effective, harmless one. It remains to be discovered.

PRACTICAL DIETETICS

IX.—WEANING DIETS

By OLIVE E. M. SHARPE, S.R.N., R.S.C.N., S.C.M.

St. Nicholas Nursery, The Hospital for Sick Children, Great Ormond Street

To wean, in the strict sense, is to feed otherwise than from the breast, but is now more commonly used when speaking of the introduction of solid food into the diet of the baby. The usual time is when the baby weighs 15 pounds (7 kg.) or reaches the age of 3 to 4 months, but in many instances the introduction of solid food by spoon begins much earlier and sometimes later.

The satisfactory progress of 'weaning' depends on patience and perseverance: patience in giving the baby time to adjust his palate to completely new tastes and textures, the feel of the spoon and solid food in the mouth; perseverance to continue giving the baby new foods slowly, repeating at a later date those that are refused at first, in spite of apparent rejection and a certain amount of resistance, which is quite normal.

The order of the introduction of solids varies. It is usual to start with a cereal mixed with the milk mixture before the 10 a.m. feed, and then to introduce vegetable purée or broth before the 2 p.m. feed. Some babies will take solids willingly before the milk feed, others demand part or whole of the milk feed first; some prefer cereals and puddings, others the more savoury broths and egg dishes—all are individuals. From an early age babies appreciate well-cooked, attractively served, appetizing meals.

CHART FOR INTRODUCTION OF SOLID FOOD

6 *a.m.*:	Breast *or* cow's milk mixture *or* dried milk mixture
10 *a.m.*:	Finely ground cereal cooked with milk or pre-cooked or processed cereal, 1 teaspoonful, increasing slowly Egg yolk, raw or coddled, 1 teaspoonful increasing to 4 teaspoonsful two or three times weekly Breast feed or milk mixture
2 *p.m.*:	Vegetable broth, homogenized broths, cooked sieved vegetables or raw sieved tomato, 1 or 2 teaspoonsful gradually increasing Fruit juice or purée, 1 or 2 teaspoonsful, gradually increasing Breast feed or milk mixture
6 *p.m.*:	As at 10 a.m. but vary the cereal and omit egg yolk Breast feed or milk mixture
10 *p.m.*:	Breast *or* cow's milk mixture *or* dried milk mixture

As the solids are tolerated and increased the milk feeds are gradually cut down in quantity and number. Some babies give up the 6 a.m. feed first, others the 10 p.m., and the feed times are gradually adjusted to the family meal times:—

On waking:	Fruit juice drink
Breakfast:	Cereal, coddled *or* scrambled egg, *or* crisp bacon Rusk or toast with butter Milk drink
Dinner:	Steamed fish, *or* minced meat, *or* steamed purée of liver, or beef, *or* grated cheese, *or* chicken Purée of vegetables—carrots, tomato, spinach, swedes, cauliflower, sprouts, potatoes Puddings: custard and fruit; purée of apple, prune, blackcurrant; milk jelly or fruit jelly; cornflour moulds. Fruit drink or water
Tea:	Baked crusts or rusk with butter. Bread and butter with honey, seedless jam, Marmite, grated cheese Fruit purée with custard or jelly. Sponge finger or biscuits Drink of milk
Bedtime:	Small drink of milk or breast feed

VITAMINS

Fruit juices can be introduced by spoon at an early age, thus preparing the baby to take from a spoon; the best time is during the afternoon. Fresh orange juice, 1 to 8 teaspoonsful, *or* concentrated orange juice, ½ to 2 teaspoonsful, sweetened with 1 teaspoonful of sugar and diluted with warm boiled water, 1 to 2 ounces (28 to 56 ml.); *or* rose-hip syrup, 2 teaspoonsful; *or* black currant juice, 2 teaspoonsful. These latter may be given on their own or diluted with water or on the cereal at the 10 a.m. and 6 p.m. feed. Cod-liver oil or the equivalent is best given before the bath, thus avoiding staining the clothes. Concentrated vitamins can be given in a spoonful of milk mixture before the 10 a.m. and 6 p.m. feeds.

RECIPES

Coddled egg.—Place egg in boiling water and remove pan from heat so that water does not boil; leave 5 to 8 minutes. White of egg is just set. Yolk only is given at beginning of weaning.

Baked crusts.—Cut white bread into thick fingers. Bake in moderate oven slowly until crisp and golden brown. Keep in airtight tin as biscuits.

Sieved tomato.—Drop tomato in boiling water, and then remove skin. Push through fine sieve with wooden spoon. Give alone, or with broth or with a little milk mixture.

Root vegetables.—Carrots, swedes, potatoes, etc. Wash and scrub to remove all earth; peel or scrape if new; rinse in cold water, and cook as soon as possible. Cut into small pieces and boil in small quantity of water until soft, strain off water. Sieve through fine sieve or through a 'Baby Mouli' grater. Use the vegetable water as basis for broth, adding a little Marmite.

Potato can be made into a purée with addition of a knob of butter and a little milk, and finely grated cheddar cheese added occasionally.

Green vegetables.—Trim off outer leaves and thick stalks. Wash thoroughly through several waters. Place in boiling water slightly salted, using as little water as possible. Cook quickly until tender. Strain off water, saving water to use for broth. Sieve through fine sieve. Margarine or butter can be added. Vegetables can be cooked in a pressure cooker.

Basic vegetable broth.—1 lb. of freshly chopped bones (to obtain bone marrow). Just cover with cold water, add pinch of salt and bring to boil. Allow to simmer for 2 hours. Strain well through muslin to ensure no pieces of bone pass through. Prepared diced vegetables can be added to broth and cooked until tender, then sieved, and flavoured with Marmite.

Steamed fish.—White fish without bones, such as fillet of sole or plaice or fresh haddock. Wash thoroughly in cold water and dry with clean cloth. Place between two plates with small knob of butter and about 2 teaspoonsful of milk. Place over saucepan of boiling water and cook until tender—about 20 to 30 minutes. Use the butter and milk to cream potatoes or make into small quantity of white sauce with cornflour. The fish can be flaked or pounded until of a cream consistency.

Beef or minced beef or liver casserole.—Calves liver is most digestible. Place about 1 oz. of meat, previously washed quickly in cold water and wiped with a clean cloth, in a small casserole dish and just cover with water. Add pinch of salt. Cook in hot oven for 1 to 2 hours until meat is quite tender. Sieve meat through 'Baby Mouli' sieve or flake with knife and fork. Add small quantity of Marmite to gravy. Vegetables can be added and cooked with meat. This recipe can be used in pressure cooking.

Puddings:—

Cornflour pudding

Cow's milk	5 ounces (142 ml.)
Cornflour	1 heaped teaspoonful
Sugar	1 teaspoonful

Mix cornflour with a little cold milk to smooth paste. Bring remainder of milk to boil and add to cornflour paste, stir well. Place in saucepan with sugar and bring to the boil and cook for 5 minutes, stirring well. Flavour with chocolate, or vanilla, or colour pink with cochineal. Can be served hot or cold as mould.

Ground rice and semolina puddings

Cow's milk	5 ounces (142 ml.)
Semolina or ground rice	1 to 2 teaspoonsful
Sugar	1 teaspoonful

Bring milk to boil and add the semolina or ground rice, beating well. Cook for 5 to 10 minutes. When cool an egg, previously well beaten, can be added, beating in slowly with a fork.

Jellies.—To vary serving of jelly:—

(1) Use fruit juices to add to value of plain jelly.

(2) Add milk instead of water to dissolved jelly.

(3) When partly set, whisk jelly with egg-whisk to stiff froth and set.

USEFUL AND INEXPENSIVE PUBLICATIONS

Most public health authorities issue helpful leaflets on weaning diets.

A very useful cookery book can be obtained from the National Association for Maternal and Child Welfare: 'The Mothers' Cookery Book', price 2*s*.

A leaflet, 'Diets for Babies and Children in Health and Sickness', is published by The National Baby Welfare Council.

A *Family Doctor* booklet, 'Nursery Feeding', is published by the British Medical Association.

REVISION CORNER

SNAKE BITE IN THE TROPICS

POISONOUS snakes, comprehensively spoken of as thanatophidians, belong to four Families.

These include the Hydrophids or sea snakes, the closely related Elapids embracing the cobras, coral snakes and related Australasian forms, and the Viperids which have two sub-families, the Viperines, the vipers or adders of the Old World, and the Crotalines or pit vipers of Further Asia and the rattle snakes and others of the New World. It would be correct to include, also, certain members of the Opisthoglyph Division of the large Colubrid Family, to which most harmless snakes belong. The snakes of this Division, the back-fanged Colubrids, are technically poisonous and have two species on record as having caused serious poisoning in man. The poison fangs of the Colubrids, Hydrophids and Elapids are grooved for the transmission of venom but those of the Viperids are more highly specialized, being completely canaliculated and thus comparable with syringe needles.

VENOMOUS SNAKES

In places where thanatophidians occur most doctors will be acquainted with the local kinds as a matter of workaday knowledge.

Notable are the coral snakes, rattle snakes and pit vipers of the Americas, the cobras, mambas and vipers (some of which are commonly called adders) of Africa, the cobras, coral snakes, vipers and pit vipers of Asia and the Elapids, related to cobras, of Australasia. No vipers or Opisthoglyphs occur in Australasia and the so-called 'death adder' of Australia itself, is in fact an Elapid. Opisthoglyphs that have been associated with serious hæmorrhagic poisoning are the tree snake or boomslang (*Dispholidus*) and the vine or tree snake (*Thelotornis*) of Africa.

Such well-known features of poisonous snakes as the hood of the cobra, the rattle of the rattle snake and the horns of certain Viperids are of course obvious labels and simplify identification. Although as a generalization, most Viperids have small scales on the head, in contrast with the larger plates characteristic of the Elapids and most harmless snakes, and although, also, head and tail shapes, and pattern and colour, may be diagnostic to the well-informed, there is only one sure way for the non-specialist to recognize a venomous snake and that is from the quite simple examination of the mouth for poison fangs. In the Elapids these are in the front of the upper jaw; they are relatively large, project prominently and are practically immovable. In the Viperids, they are also situated forward in the upper jaw but, whilst in some species they may be recognized immediately, in others, to be seen, they have to be depressed by a needle into emergence from the sheaths in which they lie folded back along the upper jaw. In the Opisthoglyphs the fangs are long and prominent, stand out midway in contrast with the other teeth in the upper jaw and are situated beneath the characteristic large eyes.

SNAKE BITE

Most bites occur on the lower part of the leg at night or in the twilight of

dusk or dawn. The over-all mortality from bites by snakes in general, is fairly low, being about 8 per cent. In most places, even with bites from the more dangerous snakes, the majority of those bitten recover, an exception being in those bitten by the krait (*Bungarus*) in India.

Bites may be from the venomous or non-venomous, and since fright may of itself have an adverse influence on health, particularly in the ultra-timid or those with heart disease, it is advisable, whenever possible, to establish the identity of the snake. Moreover, where antivenins are available, that specific to the species concerned will be required although polyvalent antivenin may be available covering all, or the more important, of the local dangerous types.

ENVENOMATION

Venom is a production of the salivary glands purposively directed to immobilization of the prey and, of course, its digestion.

It contains ferments, the toxic nature of the more important of which lies in their action as proteases destroying tissues and cells; hæmorrhagin, for example, destroys vascular endothelia, coagulase deranges clotting time, spreading factor facilitates intra-tissue spread in addition to that by the lymphatics, cholinesterase causes neuromuscular paralysis and phosphatidase causes hæmolysis.

Clinically, the nature of the poisoning may be dominated by a neurotoxic effect as in characteristic Elapid poisoning or by proteolytic effect as in that characteristic of Viperids. Many venoms contain both elements in proportions which may themselves vary considerably between species of the same genus and even between geographical races of the same species.

Inoculation of venom into a blood vessel is a more serious accident than inoculation into other tissue, and probably accounts for fatalities from bites by species not usually lethal. The amount of venom discharged from a snake will vary according to whether the bite has been with one or two fangs, whether or not it has been mechanically efficient, and the amount of venom in the snake's glands, possibly affected by recent biting, fasting, season, moulting, maturity and disease. These last conditions may affect the quality of the venom as well as its quantity. Some species, notably the saw-scaled or carpet viper (*Echis*) of India, bite more efficiently at night and this may be true also of the mole vipers (*Atractaspis*) of Africa and Nearer Asia.

In relation with the foregoing factors, the severity of poisoning clearly depends upon the amount of venom inoculated per unit of body weight. Hence children, other things being equal, are more likely than adults to be seriously affected.

SYMPTOMS AND DIAGNOSIS

An important point is identification of the snake if at all possible, for, if it is a harmless snake, reassurance of the patient is the only treatment required. The diagnosis of envenomation is clear where certain effects are apparent, especially if multiple. Such may be local pain, fang marks, local

swelling and discoloration, vomiting, salivation, sweating, vertigo, tachycardia and dilatation or contraction of the pupils, this last in poisoning by the Indian krait. Later, certain of these symptoms may exacerbate and be accompanied by bleeding into the skin, and from old or recent scars, the nose, mouth, stomach, bladder and bowels. The presence of erythrocytes in the urine may be considered presumptive evidence of envenomation provided due regard is given to other possible causes, especially in bilharzial areas and, if increasing at four-hourly urine examinations, even in bilharzial areas, strongly supports a positive diagnosis, ot which indeed it may prove the earliest confirmation. This has been noted not only in viperine poisoning but also rather surprisingly in a bite by an African cobra (*N. haje*).

TREATMENT

First-aid calls at once for reassurance to limit emotional shock, and the patient may be informed that chance is heavily on his side. Although latterly somewhat challenged, it is still conventional in most places to apply a tourniquet round a single bone above the bite, but this must not be left on for longer than, say, half-an-hour without loosening for, say, thirty seconds, owing to the danger of gangrene. The avoidance of physical agitation is recommended, together with immobilization, loose splinting, and the application of ice packs or cold water. The rationale is that the depression of muscular and biochemical activity is conducive to limitation of the speed of fixation of venom and thus more time is given for systemic adjustment and the arrival of antivenin. This is of more importance in neurotoxic poisoning. Conversely, the use of alcohol and stimulants is regarded as harmful as increasing metabolic activity. Incision and suction by cupping, as for example with a breast pump, may remove a certain amount of venom from the bitten tissue, but obviously any possible value varies inversely with the time elapsing. The rubbing in of potassium permanganate is thought to be useless and harmful. For pain, morphine or pethidine may be used, or better still 'pethilorfan' (Roche) or a similar drug. Neurotoxic envenomation contraindicates the first-named. Procaine may be used locally.

In most areas where snake bite casualties abound, antivenins specific for the local species are available and it is conventional, and best, to give them intravenously. Children require relatively rather larger doses than adults. Adrenaline should be available to counteract possible anaphylaxis.

In Elapid poisoning in which respiratory paralysis is threatening, artificial respiration or the use of an iron lung may give time for the procurement of specific antivenin and, where there is much salivation or vomiting, potential contamination or occlusion of the air-passages may require swabbing out and the inclination of the head to one side. Injections of 2 ml. of 5 per cent. sterile solution of plain soap into tissue surrounding the bite should be

given in suspected or known serious cases of neurotoxic poisoning, since this has been shown to inactivate cobra venom in some degree.

Fever may follow snake bite and in malarious areas may call for specific treatment since shock may have activated a relapse. Snakes may have infections of the mouth and antibiotics may rationally be administered, although it does not seem to have been established that the organisms concerned are pathogenic in man. It also seems rational in those obviously seriously poisoned to combine venesection from above the bitten area for the removal of vitiated and poisoned blood, with transfusion of fresh blood into another limb. This is only likely to be of value in neurotoxic poisoning within an hour or so of the bite.

The tissue destruction involved in proteolytic envenomation implies the production of histamine, and antihistaminics have accordingly been proposed as reasonable adjuvant treatment although no convincing figures have been published. Rational also may be considered the administration of intravenous ascorbic acid in those known or suspected to be on diets deficient in vitamin C, since the effects of venom hæmorrhagin and vitamin C deficiency are synergistic, and the alleviation of the one effect may subtract from the total effect. The kidneys are very sensitive to venom damage and therefore ample fluids should be given.

It is doubtful if Spartan ligaturing, incision, excision and amputation, have the slightest value after the elapse of two to ten minutes, certainly in proteolytic envenomation. They may have in neurotoxic cases, as giving time for the arrival of antivenin, for it seems that in neurotoxic poisoning fixation is not entirely irreversible whilst in that from proteolytic ferments with massive destruction of cells and endothelium, reversibility is not to be expected.

PROGNOSIS

In most Elapid bites every hour that passes is to the good and usually those recovering will do so within a day. But in krait bites there may be a most deceptive symptomless delay (eleven hours has been recorded) before the onset of rapidly serious poisoning. In typical Viperid poisoning, a good prognosis, apart from an obvious return to normal health, as judged by amelioration of systemic and local effects, is supported by a progressive decrease of hæmaturia and a trend to the three-minute level in clotting time.

CONCLUSION

Preventive measures are obvious. Where dangerous species are common stout leg coverings, a stick, and a torch at night are sensible, cracks and crevices in houses and gardens should be sealed or filled in and dwellings and outhouses should be secure against intrusion and provided with lights. Vegetation, debris, and heaps and stacks of materials are better not placed immediately adjoining residential buildings.

In treatment early specific antivenin and immobilization are most im-

portant. Reassurance of the patient is always a duty but, professionally, caution in prognosis to relatives and oneself is wise. Adult men die from bites by small specimens whilst young children may show no, or trivial, response to bites by large members of the same species. The basic factor, the amount of venom inoculated, is never known.

N. L. CORKILL, C.M.G., M.D.
Health Adviser, Aden Protectorate.

No reference has been made in this article to the problem of European vipers or sea-snake bites, as the former was dealt with by Dr. Birch in his article in the July issue of *The Practitioner* (p. 105) and the latter will be dealt with in a subsequent article in Revision Corner.

NOTES AND QUERIES

Recurrent Herpes Simplex

QUERY.—I have a patient, a male in his thirties, who has had a painful herpetic type of eruption on his lower lip during his last four summer holidays at the seaside. I presume the heat, and sea breeze must contribute to this condition. Is there any preparation that could be used to prevent this condition developing? He has used 'lipsyl' prophylactically without much success.

REPLY.—Patients suffering from recurrent herpes simplex are probably carriers of the virus and the attack may be provoked in them by many different 'triggers', the commonest being rise of body temperature but sunlight and wind may also be precipitating factors. The period of immunity following each attack is short. At present there is no known method of eradicating the virus and treatment is designed to try and increase the local resistance of the affected skin. In my experience, this is best achieved by several exposures of superficial x-ray after the attack has subsided; I give 100r (75 KV, 5 ma, no filter) to the area three times at intervals of two weeks. If a further attack should develop, although there is no adequate method of killing the virus the eruption is often unduly prolonged by secondary infection, and resolution is often hastened by the use of one of the applications containing an antibiotic and corticosteroid. The antibiotic deals with the secondary infection and the corticosteroid with the inflammatory reaction.

A suitable cream to protect against the effect of sun and wind would be cosmetically unacceptable on the lips.

H. R. VICKERS, V.R.D., M.D., F.R.C.P.

Parenteral Penicillin

QUERY.—Even in these days of penicillin V (phenoxymethylpenicillin), I often have cases in general practice for which the certainty of parenteral therapy seems desirable. When only one injection daily is possible, what is the current opinion on the most suitable form of penicillin to use? Should it be crystalline, one of the long-acting forms, or a mixture of both?

REPLY.—There is still no perfect preparation of penicillin, and it is not possible to obtain high blood levels and prolonged therapy with the same salt. In face of a serious condition, such as acute lobar pneumonia, or septicæmia, or middle-ear condition in which parenteral therapy is called for, the aim should be to kill the causal organism as quickly as possible, and this requires the quick-acting and quickly excreted material. It is still generally agreed that the blood levels should not be allowed to fall below the inhibitory concentration for the particular organism as this encourages the emergence of resistance. To reduce the number of injections necessary, a slow-acting preparation of the drug can be mixed with the injection, or an oral preparation can be given for the rest of the twenty-four hours.

The very long-acting penicillins have their place when only a single injection can be given, usually in a chronic disease with a highly sensitive organism, yaws being an excellent example. Where the population has not previously been treated with penicillin, a long-continued low blood level is effective, and taking the added risk of reactions, always associated with this type of preparation, is justified.

W. HOWARD HUGHES, M.D.

Non-Tophaceous Gout

QUERY.—In *The Practitioner* Handbook, 'Early Recognition of Disease', in the section devoted to 'Non-specific Arthritis in Adults,' the late G. R. P. Aldred-Brown discusses non-tophaceous gout, stating that the disease is not uncommon and often labelled fibrositis. Could you please let me know the modern expert opinion on the diagnosis (clinical) of non-tophaceous gout, and the most effective therapy?

REPLY.—Macroscopic tophi in gout are only visible in about 25% of an average series of cases and occur in only 2% at the first attack. Uratic deposit associated with an inflammatory reaction may occur almost anywhere, as I have shown (*Ann. rheum. Dis.*, 1950, **9**, 282), but this must not lead to the making of a loose diagnosis of a gouty 'itis' as a cause of all symptoms in anyone with a gouty diathesis. A gouty fibrositis does undoubtedly exist, however, and is suggested when a patient records acute attacks of muscle pain, tenderness and spasm, brought on by minor trauma or certain foods or drink, and especially if he also gets occasional attacks of joint pain and swelling, with complete remissions after the same trigger factors. A raised plasma uric acid with normal D.A.T. (Rose Waaler test) is confirmatory, but, especially if the patient has been taking aspirin, a normal plasma uric acid does not negative the diagnosis. A definite family history, often skipping a generation, occurs in about one-third of these cases. Rapid relief from *full* doses of colchicine, pressed to slight toxicity, is again a useful test as well as a treatment. The negative D.A.T. and absence of anæmia will help to exclude an episodic rheumatoid manifestation. Such conditions as a non-gouty allergy, disc protrusion and Neisserian infection must also be excluded. Age and sex may help to exclude or suggest the diagnosis.

Treatment will include the avoidance of particular trigger factors to which the patient is sensitive, moderate dieting, moderate but not excessive exercise, rest and protection of the affected part and elimination of definite sepsis —a factor often disregarded these days and which is the cause of some mild cases becoming fulminant. To control attacks, colchicine may be given over a long period, but the really severe attack is often better cured by full doses of phenylbutazone: 600 to 800 mg. a day for three days only. Interval treatment with uricosuric agents—salicylates, in large doses with their obvious drawbacks, probenecid for the 60% that tolerate it well, 'longacid' (a compound somewhat similar to probenecid) or 'G.28', a virtually non-toxic cousin of phenylbutazone (the last two are not yet on the general market) —is essential for all except the mildest cases with very infrequent attacks and only slightly raised plasma uric acid. For the first six weeks of administration, however, a covering dosage of colchicine should be given and it should be noted that the addition of aspirin to any of these drugs, other than the salicylates, greatly reduces their effectiveness.

G. D. KERSLEY, T.D., M.D., F.R.C.P.

Nocturnal Polyuria and Palpitations

QUERY.—A male patient, aged 74 years, with hypertension and raised non-protein nitrogen (64 mg. per cent.), suffers from attacks of nocturnal polyuria, with palpitations and exhaustion. I have tried restricting fluid, and also Rauwolfia, without any benefit. The urological surgeon can find no abnormality in his renal tract. Could you please advise me how I may cut down the frequency of these attacks? The urine is loaded with albumin but contains no casts or red blood cells.

REPLY.—Although the data provided about this patient are too incomplete to speak with confidence, the nocturnal polyuria, raised non-protein nitrogen and albuminuria without casts or red cells suggest that he has renal dysfunction secondary to hypertensive heart failure which at night is causing pulmonary congestion manifested by palpitation and exhaustion. The first step is to improve the cardiac condition by giving digitalis or digoxin, and to reduce any pulmonary œdema with a diuretic such as chlorothiazide, 0.5 g. twice daily on Mondays, Wednesdays and Fridays. Improvement in cardiac action may improve the renal function so that the non-protein nitrogen falls, and the nocturia will diminish as the heart failure goes. If the hypertension is extreme, additional hypotensive agents may be required to reduce the load on the heart. Chlorothiazide itself given over a prolonged period sometimes has a mild hypotensive effect, and the addition of Rauwolfia will add to this. Fluid intake should not be restricted.

R. I. S. BAYLISS, M.D., F.R.C.P.

Obsessional Smoking

QUERY.—I have a patient who has a well-marked obsessional ruminative thought disorder linked with smoking. Unfortunately, methods of dealing with his condition psychiatrically have only been partially successful. His intelligence does not allow of a serious psychotherapeutic approach and I have thought in terms of trying to decondition him to smoking, but have difficulty in obtaining details as to the methods that can be used.

REPLY.—I find it difficult to accept the proposition that if this patient ceases to smoke he will necessarily be relieved of his obsession. Indeed, if he is conditioned to feel disgusted or to vomit at the thought of smoking he might well develop the same reactions to the obsessional thought and add compulsive nausea to his symptoms. Replacement of the original obsession by another after a few weeks would be the most likely result. It is presumed that by 'psychiatric treatment' the inquirer means that he has taken a history and traced the origin of the obsession with the usual improvement for a few weeks, followed by relapse. He will then have met this relapse with the use of tranquillizers and drugs intended to relieve the tension associated with the obsession. This is the usual course of an obsessive ruminative state and when it is part of an obsessional personality, even in an intelligent patient, the most optimistic psychoanalyst would not embark on intensive psychotherapy. Conditioned response methods such as those which have been used for compulsive perversion are apt in the case of obsessive rumination, simply to change the content of the rumination which is likely to occur anyway with time. If the obsessive thought is spoiling the patient's life altogether, a limited leucotomy operation might give two to three years' comparative relief, but this can only be justifiable when intense distress occurs in a person of sound personality. On the other hand, it is to be remembered that long-term follow-up of very severe obsessionals shows that in the majority, spontaneous improvement occurs after several years. Although a psychiatrist is apt to feel a bit foolish discussing the matter at intervals and reassuring the patient, with no real effort to get to the heart of the problem, this reassurance is most valuable and acceptable to the obsessional patient. Most experienced psychiatrists have come to accept that, once underlying depression has been eliminated and once the temporary relief from initial catharsis has gone, supportive treatment is best in this group of patients who frequently generate almost as much distress in their doctors as they do in themselves.

Deconditioning by associating nausea with a habit is a rather drastic method of treatment and is usually reserved for addiction to alcohol. It can, however, be used for smoking. Injections of emetine or apomorphine are given in such a way that their effects come on just as the proferred cigarette is being lit. A similar aversion can be installed under hypnosis, but more than one session is almost invariably necessary if it is to be established. Better results are obtained by getting the patient to join a group who encourage and supervise each other in the difficult first stages. Such a group should be held together by a common aim other than the relief of smoking, such as preventing adolescents from taking up smoking.

PROFESSOR ALEXANDER KENNEDY, M.D., F.R.C.P., D.P.M.

Port-Wine Stains

QUERY (from a reader in Australia).—I should welcome your opinion in the case of a girl of nine months of age born with a port-wine stain of the face, and who has been told that nothing can be done for her in Australia. The parents are naturally upset about this, and are willing to bring the child to England or the United States, if they can be assured that treatment will at least ensure some improvement in the condition. I have already told them that it is generally considered that treatment in these cases is not always possible or satisfactory, but that I would seek further information through your good offices, and to that end am sending a few colour slides to illustrate the condition and would welcome your comments.

REPLY.—In most cases port-wine stain gets paler as the child gets older. Adequate make-up will always conceal a port-wine stain provided (a) that it is not of too deep a colour, and (b) that it has a smooth surface and that it does not develop bumps in it. In a girl, make-up is no problem and looking at this young lady in her photographs, I think this may well prove to be the most satisfactory solution. If make-up is not found to be useful and does not conceal the lesion, then surgery has to be resorted to with excision of the areas concerned and grafting. There may have to be a good deal of work done in this way, but probably not until the child is much older. My advice would be not to operate on a lesion of this kind unless the child has become extremely self-conscious of her lesion. There are many first-class plastic surgeons in Australia.

R. J. V. BATTLE, M.B.E., M.CH., F.R.C.S.

Chilling and Nasopharyngeal Infection

QUERY.—Is it an established fact that local lowering of skin temperature results in diminished resistance to nasopharyngeal infection (due to reflex vasoconstriction)? If this is so, then, taking the instance of a child who has had repeated episodes of generalized nasopharyngeal infection (including minor middle-ear spread), is it unwise to:—

(1) Wash his hair without subsequent thorough drying?

(2) Allow him to indulge in out-of-door activities to the point of exhaustion in cold

weather while wearing the same clothing as when indoors?

REPLY.—Chilling will reduce to a varying degree the resistance to nasopharyngeal infections. The best line of management is to increase the individual's ability to withstand moderate degrees of chilling by avoiding coddling and by encouraging the child to play in the fresh air as much as possible.

It is always unwise to wash a child's hair without subsequent thorough drying but, in the child referred to, hard continuous exercise in the fresh cold air should be carried out in the minimum of clothing consistent with comfort and the demands of the game in question.

A. A. H. GAILEY, M.D., M.R.C.P.ED., D.C.H.

Sterilization of Instruments

QUERY (from a reader in India).—(1) How long should instruments, gloves, suture materials, and so on be sterilized in steam *not* under pressure (in a perforated tray over boiling water with a well-fitting lid)?

(2) We do not possess an autoclave and have to rely on a hospital 100 miles away for our dry sterilizing. These things come in packs of double material. Can you give me any indication as to how long they can be considered sterile?

(3) Is there any danger of transmitting tetanus from one patient to another by using the same syringe and needle for injections, after boiling for 20 minutes? Is it necessary to keep a separate set of injection equipment for tetanus patients?

REPLY.—Sterilization is an absolute term which implies the killing of all living micro-organisms including spores. One of the most efficient methods of sterilization is by exposure to saturated steam for certain combinations of time and temperature, e.g. 130°C. for two minutes, or 126°C. for ten minutes. Saturated steam below a temperature of 115°C. cannot be guaranteed to kill all spores unless the exposure is prolonged. Excluding contamination with spores, most pathogenic vegetative organisms can be killed by exposure to moist heat at lower temperatures. The method of sterilization and the temperature and exposure times needed will vary with the material to be sterilized. For instance, clean instruments can be sterilized much more quickly than gloves. Some suture materials are destroyed by heat and their methods of sterilization are usually described by the manufacturers.

In answer to the questions:—

(1) Steaming, as described, is very unreliable as the temperature may vary considerably within the chamber. Instruments and gloves should be thoroughly cleaned and then boiled in soft water for ten minutes. Vegetative pathogenic organisms will not survive this treatment. If the hospital is above sea level the time should be extended to allow for the depression of the boiling point with increased altitude.

(2) If the packs are initially sterile and dry and kept dry they will remain sterile indefinitely, provided that they are hermetically sealed so that dirt and insects cannot enter.

(3) Tetanus spores will not be killed by boiling for twenty minutes. The sterilizing power of boiling water is enhanced by the addition of 2% washing soda (Na_2Co_3) and it has been claimed that this will deal with spores in ten to thirty minutes, but exposure to moist heat at higher temperatures is preferred by most authorities.

The essential preliminary to sterilizing syringes is their proper cleansing for which a non-ionizing detergent can be used. If the syringes are clean and sterile then there will be no risk of transmitting the tetanus. It is impossible to assess the risks when using equipment which is not sterile.

E. J. K. PENIKETT, M.B.

Call System for Patients

DR. G. S. ADAMS, Honorary Secretary of the Practice Equipment and Premises Committee of the College of General Practitioners, writes:—A Group Surgery for three doctors with a single waiting room has been built. They do not wish to employ a secretary or receptionist and the method of calling patients from the waiting room to the individual Consulting Rooms has raised a problem.

Many doctors must have had a similar problem to solve, and I wonder whether they would be good enough to drop me a line, giving their solutions, at The College of General Practitioners, 41 Cadogan Gardens, London, S.W.3.

Thrombophlebitis

DR. S. CLIFFORD ROGERS writes:—I would like to protest against the absence from the symposium on 'Diseases of the Veins' in the July issue of any mention of what is the most important advance in this field in the last two years to the general practitioner. I refer, of course, to the symptomatic treatment of superficial venous thrombosis with phenylbutazone in the small dose of 100 mg. three times daily. This treatment has, in my experience, greatly hastened the relief of pain and the resolution of perivenous inflammation and also seems most effective in preventing the spread of thrombosis to adjoining segments of dilated veins. This consistently good response has relieved the general

practitioner of most of the anxiety of treating these cases which previously were an endless source of trouble and worry.

REPLY.—The action of phenylbutazone in relieving pain is well recognized; it is often as good as that of salicylate and codeine but rarely better. If the drug alters the natural history of thrombophlebitis (and there do not seem to have been adequate controlled trials to make sure of this point) it would appear to do so by virtue of its effect as an anticoagulant—an effect which, like that of salicylates, is variable and unpredictable. Unfortunately, phenylbutazone is a much more dangerous drug than salicylates.

H. A. DEWAR, M.D., F.R.C.P.

A Holiday in Brittany

MR. VIVIAN ROWE (*Deputy Director of the French Government Tourist Office*) writes:—My attention has been drawn to the query and reply in the July issue regarding 'A Holiday in Brittany' (p. 111). We are distressed that a medical man of Dr. Douthwaite's eminence should still be convinced that drinking water in France is no safer than it was half a century ago. In fact, urban supplies have for a number of years been comparable to those in this country. Pasteurized milk is available throughout France. The average number of British tourists holidaying each year in France is of the order of three-quarters of a million. The number of cases of typhoid as a result of their journey in France is so infinitesimal as to be properly considered as non-existent. It does seem really regrettable that Dr. Douthwaite should make a holiday in France sound the most perilous of adventures.

REPLY.—I never suggested that the drinking water is not safer in France than it was half a century ago; neither did I make any special reference to urban supplies which are, of course, in general as safe as here. Your correspondent proposed going to Brittany where the water in some places is certainly not of the standard of purity which would allow its drinking without the precautions which I have advised. No matter how many people go to France without getting typhoid, the fact is that since the last war I have seen five cases of typhoid or paratyphoid acquired in that country. The figure is not negligible when one considers that I am merely one physician among many. I go to France with great regularity but take the precautions which I advised to your correspondent. Incidentally, it must be remembered that this letter was written for medical people and none of them would regard a holiday in France on the strength of my letter as a perilous adventure. If I were writing for lay people of course one would have to put in all sorts of qualifications. I know that pasteurized milk is available, but the point is that, as I wrote, the milk must not be *assumed* to be pasteurized.

I can detect no statement in my letter which is incorrect or unfair.

A. H. DOUTHWAITE, M.D., F.R.C.P.

PRACTICAL NOTES

Angina Pectoris

IN discussing the diagnosis of angina pectoris, Tinsley R. Harrison (*Bulletin of the Johns Hopkins Hospital*, June 1959, **104**, 275) expresses the opinion that 'there are many patients in whom the response to glyceryl trinitrate is of crucial importance'. He draws attention, however, to 'some of the pitfalls which may trap the unwary'. In the first place there are what might be described as 'false positives': i.e. relief of non-anginal pain. This may be due to spontaneous relief of the pain coinciding with the administration of the nitroglycerin. Such a pitfall can be avoided by some form of control. Attention is also drawn to the fact that the relief of non-anginal pain is seldom rapid and complete. The second pitfall is the apparent failure of nitroglycerin to relieve the pain of angina. This may be due to inadequate dosage (sufficient must be given to induce headache or flushing) or deterioration of the drug. The other possibility is that the pain is that of a myocardial infarction or 'pre-infarction' pain.

In discussing treatment he draws attention to the value of inunction of an ointment containing glyceryl trinitrate. He reports having seen 'many patients whose attacks are reduced by 90% or more within twenty-four hours by the use of nitroglycerin ointment applied every two to six hours'. The indications for such treatment are frequent attacks at rest, especially nocturnal; status anginosus; pre-infarctional angina. The dosage is 'that amount which is not quite enough to cause headache', and it is spread thinly (not rubbed) on the chest, abdomen or thighs every three to six hours. In the case of nocturnal angina it is applied at bedtime, and if necessary about four hours later, to prevent attacks.

Trifluoperazine in Vomiting of Pregnancy

SATISFACTORY results are reported by G. W.

Prueter (*Canadian Medical Association Journal*, July 1, 1959, **81**, 21) from the use of trifluoperazine in the treatment of the nausea and vomiting of pregnancy. His conclusions are based upon his findings in a series of 70 pregnant women—21 primiparæ and 49 multiparæ. All of the latter had had nausea and vomiting in previous pregnancies, and five of them had had to be admitted to hospital for pernicious vomiting in a previous pregnancy. All of the women had failed to respond to reassurance and dietetic treatment. The initial dosage was 2 mg. two, three or, rarely, four times daily. This was gradually reduced. Treatment was continued for an average of four to six weeks. Usually, within a week or two, patients reported that they were 'getting along quite well' on two 2-mg. tablets daily: one at breakfast and one at bedtime. The over-all results were that 51 women obtained complete relief, and 12 'partial but acceptable relief', whilst seven obtained no relief. All but one of the multiparæ and 15 of the 21 primiparæ had good responses.

Strontium Lactate in Osteoporosis

STRONTIUM lactate is of value in the treatment of osteoporosis, according to F. E. McCaslin, Jr., and J. M. Janes (*Proceedings of the Staff Meetings of the Mayo Clinic*, June 24, 1959, **34**, 329). This conclusion is based upon a review of 32 patients, whose ages ranged from 34 to 78 (average 56 years). All but four were women. Half the patients had had their symptoms for more than a year. Eight of the patients were mildly affected, 21 were severely affected but ambulant, and three were bedridden. The dose of strontium lactate was 6.4 g. daily in divided doses. Treatment was continued for periods ranging from three months to three years. Of the 32 patients, 22 were treated with strontium lactate alone and 10 with a combination of strontium lactate, œstrogens and testosterone. Of this latter group, nine experienced 'marked subjective improvement' and one 'moderate improvement'. Of the 22 treated with strontium lactate alone, 18 'improved markedly' and four 'improved moderately' by subjective standards. In 25 patients (78%) comparative x-rays of the lumbar and thoracic vertebræ showed 'equivocal changes'. The rationale of this use of strontium is that it increases the retention of calcium in bone.

Prednisone in Primary Tuberculosis

THE value of prednisone has been investigated by K. W. Lavers and J. C. Roberts (*Tubercle*, June 1959, **40**, 173) in 10 children, aged 18 months to 10½ years with primary pulmonary tuberculosis, in whom the process, despite antituberculous drugs, seemed to show either no change or worsening. Chemotherapy consisted of either streptomycin and isoniazid or PAS and isoniazid. The dosage of streptomycin was 0.25 g. daily for smaller children and 0.5 g. daily for the larger ones. The dosage of isoniazid was 50 mg. for the small ones and up to 200 mg. daily for the larger ones. PAS was given in 2 to 3 g. doses daily for the smaller children, and up to 10 g. daily for the larger ones. The dosage of prednisone was 2.5 mg. daily for children of 4 years and under, and 5 mg. for the older ones. Improvement occurred in eight patients, in seven of whom prednisone was considered to have influenced this. 'On the whole', it is stated, 'the improvement which occurred with prednisone therapy was neither rapid nor dramatic. This may in part be due to the small doses employed. In no case did deterioration of a lesion occur while prednisone was given, and in no case was it thought that any ill-effect resulted from the use of the steroid'. There were no significant side-effects. Slight mooning of the face developed in two children, in one of whom it was accompanied by weight increase.

Orphenadrine in Parkinsonism

As a result of their experience with its use in 125 cases, S. Rosenfeld and his colleagues (*Journal of the American Geriatrics Society*, June 1959, **7**, 502) consider that orphenadrine ('disipal') is 'most effective as an adjuvant' in the treatment of Parkinsonism. The dosage is 50 mg. thrice daily. They give details of the results obtained in a series of 21 patients, aged 41 to 77, who had previously failed to obtain satisfactory relief from other anti-Parkinsonism agents. Orphenadrine was given without alteration of the pre-existent medical regimen. The drug was tolerated well and there were no significant side-effects. The most striking benefit was the improvement in emotional status, with reduction of depression. Twelve of the 16 patients who had previously been depressed became 'distinctly affable', and another two, in whom no obvious improvement was noted in this respect, asked for further treatment because the tablets made them 'feel better'. The next most striking effect was in sialorrhœa: in 10 of the 18 patients with this disturbance there was 'mild to marked improvement'. It had little effect in oculogyric crises and none on tremor, but 11 of the 21 patients with rigidity experienced mild to marked relief of this symptom.

Isolation of Infants with Thrush

As a result of an investigation carried out on 1,622 consecutive new-born infants, P. J. Kozinn and his colleagues (*Journal of the American Medical Association*, July 4, 1959, **170**, 1172)

conclude that 'physical isolation of infants with thrush does not warrant its high direct and indirect costs to the hospital since such procedures neither prevent nor protect the nursery population from exposure to the disease'. During the six months' investigation three isolation periods alternated with three segregation periods. During the latter all infants with oral thrush were segregated on the side of the large general nursery, whilst during the isolation period all infants with oral thrush were sent to the isolation nursery immediately on detection of the condition. The results showed that the incidence of thrush was higher in the isolation group than in the segregation group, and that the incidence of Candida infection was not increased in infants located next to, or in the same section as, infants with latent thrush (i.e. infants who yielded *C. albicans* on culture in hospital but did not develop clinical manifestations up to the 16th day of life). It is stressed that candidiasis is not an airborne infection, and that the majority of new-born infants who develop the condition have contracted the infection at birth before they are ever admitted to the nursery.

Surgery and Intractable Pain

THE place of surgery in the management of intractable pain is discussed by John E. A. O'Connell, of St. Bartholomew's Hospital (*British Journal of Surgery*, May 1959, **46**, 608), on the basis of his findings in 100 patients suffering from intractable pain and treated by various operations upon the central nervous system. In 87 patients the pain was due to malignant disease. A total of 104 operations was performed: rhizotomy on 19 occasions, prefrontal leucotomy on five occasions, and anterolateral chordotomy on 80 occasions. Among the 94 patients who survived the operation, complete relief was obtained in 58 (62%), relief with recurrence in 22 (33%), whilst in 14 (15%) pain was relieved only in part or not at all. The view is expressed that 'surgery should be reserved for cases in which pain is severe and unresponsive to simpler measures. It should be withheld when life expectancy is so short that the suffering occasioned by the operation would persist through the period of survival'. The minimum life expectancy justifying operation is twelve weeks. Contraindications to surgery include drug addiction, psychogenic pain, and the presence of other factors such as an enlarging tumour, discharge from an infected ulcer, and fistulæ involving the pelvic viscera. In the presence of these distressing factors it is so often difficult to assess the relative significance of the pain.

Of prefrontal leucotomy it is said: 'The pain remains but the personality is so altered that the sensation ceases to carry any unpleasant significance. While the patient is doubtless unaware of the change it can be extremely distressing to his family who suffer a double deprivation—the loss of the known and loved personality being followed after an interval by death in the usual sense of the word. This form of therapy must clearly be avoided whenever possible and instituted only as a last resort after full explanation of its implications to the family'.

Epiphora

IN a series of about 350 cases of epiphora referred to a special clinic, H. Basil Jacobs (*British Journal of Ophthalmology*, June 1959, **43**, 332) reports that 14 'appeared to be associated with weakness of the orbicularis oculi, and were benefited by exercising the lid muscles'. The diagnosis of weak lid muscles is difficult and rests on a favourable response to exercises and the failure of other accepted methods of treatment. Dynamometer readings of the strength of the muscles are not always helpful as high measurements may be obtained in patients in whom the muscle tone appears to be deficient clinically. Lower lids that are pitched below the normal level or feel unduly slack in tone, and puncta out of position are useful but not wholly reliable clinical guides'. The patient is instructed to exercise the muscles by a slow sustained winking movement or a straining visual effort twenty times, thrice daily. It is important to avoid forcible lid closure, as the upper lid may catch behind the lower, everting the punctum. In some cases the treatment has to be continued for some months, and occasionally it is necessary to supplement it with faradism.

Amenorrhœa and Liver Disease

ATTENTION is drawn by Paul Green and Leon Rubin (*American Journal of Obstetrics and Gynecology*, July 1959, **78**, 141) to the fact that amenorrhœa may be the presenting manifestation of chronic liver disease. Details are given of 18 cases of amenorrhœa associated with chronic liver disease, the ages of the patients ranging from 17 to 40. In all the cases flocculation screening tests for the presence of liver disease were strongly positive. The etiology of the liver disease varied considerably: in seven it was unknown, in eight it was the sequel of infectious hepatitis, in two it was due to alcoholism, and in one it was associated with disseminated lupus erythematosus. Why amenorrhœa develops in these patients is not clear, but it is considered likely to be linked with the known association between œstrogen metabolism and the liver.

REVIEWS OF BOOKS

Cancer: Diagnosis and Treatment. Edited by JOHN B. FIELD, M.D., PH.D. London: J. & A. Churchill Ltd., 1959. Pp. xv and 796. Illustrated. Price £6 10*s.*

THE editor has planned a balanced treatise on all facets of the clinical problems in cancer, and to this end his team of recognized authorities contribute compact reviews on their specialties. Allegedly the volume is not weighted for or against surgery or radiotherapy, yet of the twenty-eight contributions only one is by a radiotherapist. Despite this, the text preserves a reasonably fair balance. Throughout, the clinical sections of the chapters are excellent, and this especially applies to the accounts of tumours of the female generative tract. The choice of treatment for cancer of the uterine cervix is summarized: 'in spite of the recent return to radical surgery, radiation therapy is still the best method except in special cases'. Tumours of the breast by C. D. Haagensen presents an excellent review of the problems; it is doubtful if his advocacy of 'self-examination of the breast' as an aid to early diagnosis of cancer will appeal to women or practitioners in this country. Haagensen's results with radical mastectomy for carcinoma of the breast are extremely good, being based upon a return to the technique of Halsted, allowing up to five hours for the operation. Summary dismissal of McWhirter's technique of local mastectomy and x-ray therapy at Edinburgh is disappointing.

This volume provides in a well-presented and succinct form, up-to-date information on the diagnosis, treatment and prognosis of malignant disease, and should prove a useful reference book for the general practitioner.

A System of Orthopædics and Fractures. By A. GRAHAM APLEY, M.B., B.S., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1959. Pp. vii and 376. Price 47*s.* 6*d.*

THE author has almost achieved the impossible: he has nearly contained a quart in a pint pot. To manage this he has, of course, had to do without illustrations but he has overcome this deficiency by providing concise accurate word pictures. Throughout, the influence and teaching of George Perkins can be detected. From the diagnostic standpoint this book is excellent —the clinician is introduced to a methodical approach and is instructed to 'look', 'feel', and 'move' and his findings are recorded under these headings. The restricted space, however, does not allow for detailed treatment and, although current views are put forward, some may be criticized. Thus anti-gas-gangrene serum is recommended as a routine administration in open fractures; bone grafting is proposed for delayed union of the fractured navicular; the contraindications given for operations on meningoceles are no longer valid. The text is based on a series of lectures for the final F.R.C.S. examination and from this point of view it is invaluable. Despite its excellence the script cannot help suffering from brevity, and the book as a whole may be considered as an elaborate synopsis. This, however, is compensated by the provision of a bibliography for further reading.

The book may be too concentrated and advanced for the undergraduate student but it should be read by all those working for the final F.R.C.S. examination. It will also appeal to the doctor who wishes to grasp the essentials of an unfamiliar subject quickly, and to the orthopædic surgeon wishing to refresh his memory and for lecture purposes.

A Guide to Orthopædics. By T. T. STAMM, M.B., F.R.C.S. Oxford: Blackwell Scientific Publications, 1958. Pp. 115. Figures 19. Price 12*s.* 6*d.*

THE author has written this little book for the benefit of those on the fringe of the truly specialist aspect of orthopædic surgery. For this reason he has confined himself to those parts of the subject especially of interest to physiotherapists, school doctors, health visitors, and other non-specialists. It is an excellent book. Brief, lucid, and sensible; it has a way of explaining to specialist and non-specialist alike, in simple style, many of those minor problems of the subject that we accept as problems and pass on without trying to solve them for ourselves. This book should be on the practitioners' bed-side table.

Surgery of the Prostate. BY HENRY M. WEYRAUCH, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders Co., 1959. Pp. xii and 535. Figures 288. Price £5 5*s.*

AN excellent book and beautifully produced in every way. In view of the frequent references to various authorities which occur in the text it seems a pity that room has not been found for a tabulated list of references at the end of the book or possibly at the end of each chapter. This point is emphasized as the book will form part of the armamentarium of urologists who are likely to require elaboration of particular points. Incidentally, the book appears to offer a convincing answer to those who are foolish enough to inquire why urology should

be considered a specialty. Minor errors occur from time to time, but no doubt these will be corrected in a subsequent edition.

The book contains much valuable practical advice and is the result of the author's personal experience, which is wide. He does not attempt to push any particular method of treatment to the exclusion of all others. This book can be confidently recommended and should be on every surgeon's bookshelf.

Physical Diagnosis. By JOHN A. PRIOR, M.D., and JACK S. SILBERSTEIN, M.D. London: Henry Kimpton, 1959. Pp. 388. Figures 193. Price 56*s*.

THERE is a large and increasing number of books, chiefly from the United States, concerned with history-taking and physical examination. As they are written for the student when he is first in contact with patients the subject-matter is largely standardized, but they vary in their presentation and emphasis according to the practice of the medical school at which the authors teach. This one, from the Ohio State University College of Medicine, measures up well to its competitors, with its strong emphasis on the taking of a good history and the value of information which can be acquired without special aids to diagnosis. It draws strength from the numerous illustrations which are good and are easily understood, and from the clarity of the descriptions of clinical methods. The examination of all systems is described, with the notable exception of psychiatric history taking, of which no mention is made.

This is not a book to which reference will often be made by the student once his elementary days are over, but while they are on, its simplicity will make it valuable to him. This simplicity also narrows the gap across the Atlantic so that the book will fit in with the pattern of elementary teaching usually followed in this country.

The Organic Psychoses: A Guide to Diagnosis. By JOHN G. DEWAN, M.D., D.P.M., F.R.C.P.(C), F.A.C.P., F.A.P.A., and WILLIAM B. SPAULDING, M.D., F.R.C.P.(C). University of Toronto Press. London: Oxford University Press, 1959. Pp. xiii and 170. Price 48*s*.

A PSYCHIATRIST and an internist, who are both university teachers, have collaborated in producing a small work designed to enable the practitioner, the medical registrar or the psychiatrist to diagnose the different types of confusion and dementia found in practice. Physical conditions which can be responsible for supposedly functional nervous and mental conditions are also discussed. Such conditions are classified and the laboratory tests which are usually carried out are listed. A practical account is given of the clinical approach to such cases, with illustrative cases, and there is a full bibliography. The book is warmly recommended as illuminating a field where misdiagnosis is particularly common.

The Principles and Practice of Electrotherapy and Actinotherapy. By BRYAN O. SCOTT, M.R.C.S., L.R.C.P., D.PHYS.MED. London: William Heinemann Medical Books Ltd., 1959. Pp. viii and 314. Figures 168. Price 27*s*. 6*d*.

Therapeutic Electricity and Ultraviolet Radiation. Edited by SIDNEY LICHT, M.D. New Haven, Connecticut: Elizabeth Licht, 1959. Pp. xii and 373. Figures 94. Price $10.

DR. SCOTT'S book is written for students preparing for the examinations of the Chartered Society of Physiotherapy. The author aims at covering the various aspects of the syllabus of the Society, and in this he succeeds admirably. He systematically covers the physical, mechanical and technical aspects of the therapeutic electricity and certain electromagnetic radiations. He correlates the physical properties of these forms of energy with their application to treatment. In his conclusions on therapeutic effects he shows considerable tact, for much persists in the technical lore of the physiotherapist that no longer can be accepted by the medical profession; whilst not hesitating to reject outworn claims he does so reasonably and gently. As he says in his preface his book will help doctors interested in physical medicine as well as students of physiotherapy.

DR. LICHT'S volume considers two traditional forms of physiotherapy which have been employed in an empirical fashion for many years. It is surprising how little new the authors find to say about either of them. Although the book is expensive and one-quarter is devoted to mainly irrelevant historical data, it will certainly provide a good introduction to electrotherapy and ultra-violet radiation for anyone taking up the study of physical medicine. The basic physics involved are authoritatively dealt with by Stuart Reiner and William Anderson Jr., whilst the clinical aspects are adequately covered from the theoretical and practical standpoints. In a further effort at comprehensiveness the editor has included a chapter from Moscow on electro-sleep. This book would have had a wider appeal if it had been more modestly produced.

The School Health Service. By S. LEFF, M.D., D.P.H., and VERA LEFF. London: H. K. Lewis & Co. Ltd., 1959. Pp. viii and 316. Price 30*s.*

THE fiftieth anniversary of the founding of the School Health Service is an obvious occasion for the production of a history and critical appraisal of that Service. The authors of this book have gone a long way towards providing such a history and appraisal and are to be complimented on the industry which has gone into its making. The book is clearly intended for a mixed readership, as it should be, for it is important that more than doctors should have an idea of what the Service is and what it is trying to do; it is sufficiently technical to be of use to doctors but should be quite comprehensible to teachers, social workers and lay members of local authority committees.

It begins by sketching the general history of the Service, but rather more than half of its pages record and discuss the development of the various techniques and practices. The brief chapter on the future of the Service with which the book ends is slender in itself but this does not greatly matter since the technical chapters include many constructive suggestions. The criticisms are reasoned and fair, though perhaps more attention might have been given to some of the experiments which are going on in the Service. The book is well documented but would have been improved by a bibliography in addition to the list of references. On the debit side must be recorded a good deal of carelessness. An important official body has different names on consecutive pages, a source document has different titles in the text and in the list of references and the English is often slipshod; faults like this do not make for easy reading and might make it easy to underrate the book's very real worth.

Psychology as Applied to Nursing. By ANDREW MCGHIE, M.A. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. xii and 247. Price 17*s.* 6*d.*

THE General Nursing Council now include psychology in the syllabus for their preliminary examination; and, with commendable insight, suggest that the nurse should know how to deal with his or her own problems, as well as how to study the patient as a person. The author of this book—a senior clinical psychologist and a lecturer in psychology at the Royal College of Nursing (Edinburgh)—aims to give his readers the kind of information and viewpoint that should help them to do this. He gives a good account, psychodynamically orientated though free from special pleading, of individual psychological progress from the cradle to the grave and of the intercurrent disturbances, including illness in general, which may beset it. This occupies nearly half of the book. The rest deals with human motivation, the relative roles of heredity and environment, cognitive functions and social psychology, including group morale and leadership. At the end of each chapter are a few test questions, chiefly to encourage the reader to formulate her ideas but also to indicate the sort of question that might appear in an examination. Yet this is no cram-book, nor on the other hand is it fully compendious as a work of reference might be. Although somewhat wordy, it is an original presentation of a difficult subject. If it is read slowly and contemplatively it is likely to stimulate thoughtful nurses—seniors no less than students—to think in a new and better-informed way about their patients and themselves, to their mutual benefit—and incidentally enhance their chances of success in examinations. It deserves a place in the library of every training school for nurses.

The New Frontier—Man's Survival in the Sky. By K. G. WILLIAMS, M.R.C.S., ASSOC. M. I. MECH. E. London: William Heinemann Medical Books Ltd., 1959. Pp. vii and 161. Illustrations 56. Price 21*s.*

THIS admirable little book describes in intelligent layman's language the physiological and psychological problems encountered in aviation and space-flight. The author draws largely on British Service and civil experience to give a clear account of the way these problems have been, or might be, solved. The style is that of a series of personal lectures, and this impression is reinforced by the blackboard-type line drawings, which are the book's only illustrations. Unfortunately, a few are over-simplified, and their clarity suffers thereby. The book is fully up-to-date with the sole exception of the section on radiation, where important new data from satellite and space probes could not be included. Doctors, scientists and technicians will find this a useful guide to man's place and limitations in flying and the Space Age.

Shakespeare and Medicine. BY R. R. SIMPSON, M.B., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. vii and 267. Price 25*s.*

THIS labour of love by a devout Shakespearean is a most attractive book. To fellow-devotees it will provide matter for many a discussion. To the philistine, who believes that there are other equally great names in English literature, it will come as a revelation how many medical references are to be found in his plays. To the

post-prandial speaker seeking an appropriate quotation to impress his bemused medical audience it will prove a veritable boon. It is, of course, a tribute to the genius of Shakespeare that a book such as this should have a wide appeal, but doctor-readers will be quick to recognize in the author a member of their profession who ranks high in the hierarchy of Shakespearean students.

To many readers, the most interesting chapter will be that devoted to 'Shakespeare and the influence of his son-in-law, Mr. John Hall, Physician', but the many other chapters on Shakespeare and pregnancy, children, old age, eyes, ear, nose and throat, and venereal diseases are little masterpieces of succinct exposition.

NEW EDITIONS

Major Endocrine Disorders, by S. Leonard Simpson, M.D., F.R.C.P., A. Stuart Mason, M.D., M.R.C.P., and G. I. M. Swyer, D.M., M.R.C.P., third edition (Oxford University Press, 50*s*.).—The first edition of this book stuck fairly closely to its title. The third has left its title behind (for it includes minor endocrine disorders) and is proportionately the more valuable. It is an excellent short review of clinical endocrinology suitable for all medical readers except perhaps endocrinologists. It is inevitable that a reviewer of a book which boils down so large a subject so successfully to its essence will find points to criticize, but they are remarkably few and unimportant. It can sincerely be recommended to general physicians, general practitioners and medical students, for it includes everything important which should by now have filtered through into the main stream of medicine, but too often has remained in the private waters of the specialist.

Textbook of Pediatrics, edited by Waldo E. Nelson, M.D., D.Sc. (W. B. Saunders Company, £5 15*s*. 6*d*.).—The seventh edition of this well-known American textbook is quite remarkably up-to-date, in spite of which it is somewhat shorter than its immediate predecessor. It is beautifully produced, although too heavy to hold comfortably for long periods. The illustrations are mostly excellent and well-chosen. The claim of its editor that it approximates to complete coverage of pædiatrics is well-founded. Its numerous contributors have achieved a consistently high standard with a minimum of overlapping. A common criticism of American textbooks that the many references to the literature are too exclusively from American sources is valid here. This is unfortunate because there must be few departments of pædiatrics or individual pædiatricians throughout the English-speaking world not in possession of 'a Nelson'. It is now *the* recognized textbook of reference in its specialty. In fact, it could fairly claim to be the best pædiatric treatise in the world. The latest edition has improved upon its forerunners. It is a book which every physician (or surgeon) whose work involves the care of sick children must possess.

A Synopsis of Anæsthesia, by Alfred J. Lee, D.A., F.F.A.R.C.S., fourth edition (John Wright & Sons Ltd., 27*s*. 6*d*.).—The latest edition of this famous book is fully up to the standard of previous ones. The whole book has been revised and very complete references are given, so that the reader may enlarge his knowledge by further reading if he so desires. Indeed, the author suggests in his preface that he hopes that this book will serve as a stimulant to further reading. Two new chapters have been added, one on the phenothiazine derivatives and an excellent one on hypothermia. There is a wealth of information packed into some 600 pages, with remarkably few typographical errors. It would be well, however, if B. G. B. Lucas's name had been printed correctly (pp. 31 and 533), but this is only a small printing error easily corrected. This latest edition should be on the bookshelf of every anæsthetist.

Notable Names in Medicine and Surgery, by Hamilton Bailey, F.R.C.S., and W. J. Bishop, F.L.A., in its third edition (H. K. Lewis & Co. Ltd., 35*s*.), shows a rather better balance between medicine and surgery. As the authors are at pains to point out, it is not a history of medicine, but merely a list of biographical notes of the men whose names are commonly met in practice, e.g. Addison, Bright, Hodgkin and Ménière. For this limited purpose it is an admirable book, providing the student with the essential details about those whose names he is continually hearing during his training. Of the 79 people dealt with, all deserve a place. The only criticism of the new edition is the inclusion of footnotes. This is a retrograde step which does nothing to enhance the value of a book which can otherwise be recommended without hesitation.

The contents of the October issue, which will be a special number devoted to 'Advances in Treatment,' will be found on page A 118 at the end of the advertisement section.

Notes and Preparations see page 369.
Notes from the Continent see page 373.
Fifty Years Ago see page 375.
Motoring Notes see page A 89.
Travel Notes see page A 93.
Bridge Notes see page A 97.

NOTES AND PREPARATIONS

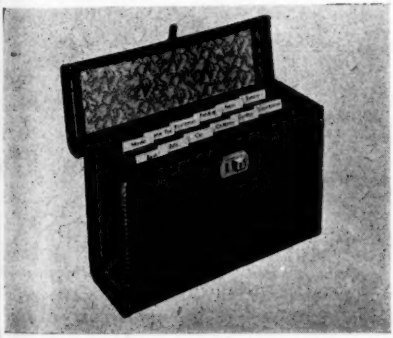
NEW PREPARATION

'ALBAMYCIN GU' tablets each contain 125 mg. of 'albamycin' (novobiocin as the calcium salt) and 250 mg. of sulphamethizole. They are indicated in acute and chronic, single and mixed infections of the urinary tract, 'even in the presence of resistant organisms or urinary retention', and are said to be bactericidal both within and without the urinary tract. Available in bottles of 30 and 100 tablets. (Upjohn of England Ltd., Fleming Way, Crawley, Sussex.)

'AMPHACTIL' tablets each contain 25 mg. of chlorpromazine hydrochloride B.P., and 5 mg. of dexamphetamine sulphate B.P., and are intended for the treatment of mild depressive states with anxiety, and for 'the relief of pain associated with a psychogenic factor'. Issued in containers of 50 and 500 magenta-coloured, sugar-coated tablets. (Pharmaceutical Specialities (May & Baker) Ltd., Dagenham, Essex.)

NEW APPARATUS

'NATIONAL HOMEFILE' is a 'strong, travel-tested fibre case' containing twelve files and measuring 16½ × 11½ × 6½ inches (price £2 17*s.* 9*d.*). As shown in the illustration, the files have suitable 'home' titles but alternative printed titles and plain labels can be supplied to suit individual



needs. Also available is the 'National Personal File' which is a strong steel case measuring 16½ × 11½ × 7½ inches, containing twenty-five titled files suspended on slide rails, with a spring clip in the lid (price £5 5*s.* 5*d.*). (National Loose Leaf Co. Ltd., 27 Cursitor Street, London, E.C.4.)

PHARMACEUTICAL NOTES

BURROUGHS WELLCOME & Co. announce that 'darenthin' tablets, each containing 200 mg. of bretylium tosylate, are now generally available. Issued in bottles of 100 and 500 compression-coated tablets. (The Wellcome Building, Euston Road, London, N.W.1.)

THE DISTILLERS CO. (BIOCHEMICALS) LTD. announce the introduction of 'distaquaine V-K suspension' which is a 'ready-prepared suspension' of phenoxymethylpenicillin as the potassium salt. Issued in bottles of 60 ml. containing 125 mg. in each 5-ml. teaspoonful. (Broadway House, The Broadway, Wimbledon, London, S.W.19.)

H. R. NAPP LTD. announce the addition of 100 mg. of ascorbic acid to the formula of their 'caapi' anti-coryza tablets. (3 & 4 Clements Inn, London, W.C.2.)

SYMPOSIA

Chronic Bronchitis will be the subject of a symposium organized by the Chest and Heart Association, to be held in the Lecture Hall, Ashludie Chest Hospital, Monifieth, at 9.45 a.m. on Sunday, September 27, 1959. Further details may be obtained from the Scottish branch of the Association at 65 Castle Street, Edinburgh, 2.

Biological Problems Arising from the Control of Pests and Diseases will be the subject of a symposium organized by the Institute of Biology, to be held in the Lecture Hall, Royal Geographical Society, Kensington Gore, London, S.W.7, on October 1 and 2, 1959. Further details may be obtained from the Institute of Biology, 41 Queen's Gate, London, S.W.7.

COMPETITION

The Cause and Care of the Post-Thrombotic Leg will be the subject for the 1959 competition for the National Varicose Foundation Silver Medal which is open to all registered medical practitioners resident within the British Isles. Full details may be obtained from the Secretary of the Foundation at 5 Park Lane, Wembley, Middlesex.

EXHIBITION

THE *Royal Northern Hospital Annual Clinical Exhibition* will be held at the hospital during the week beginning October 19, 1959, from 9 a.m. to 9 p.m. Exhibits of medical and surgical interest will be mounted by members of the staff of the hospital and each evening films of current interest will be shown at 8.30 p.m. and followed by refreshments. All practitioners will be welcome.

EMERGENCY BED SERVICE

THE Emergency Bed Service of the King Edward's Hospital Fund for London comes of age this year, and the annual report of the Service for the year ended March 31, 1959, which has recently been published, contains some interesting comparisons of the work of the Service 'then' and now. During its first year the Service handled a total of 8,309 cases —some 500 fewer than those dealt with in one month (February) in the period covered by the current report. During this period the Service received 63,807 applications for admission to hospital. Concern is again expressed at the increasing number of instances in which the Service is asked to arrange last-minute admission for normal maternity cases, whose home conditions make a hospital confinement necessary. In the year under review there were 2,591 such cases, compared with 1,699 in the previous year.

NEW *J.A.M.A.* EDITOR

DR. JOHN H. TALBOTT, professor of medicine in the University of Buffalo School of Medicine, has been appointed editor of the *Journal of the American Medical Association*. He will also be director of the A.M.A.'s division of scientific publications. Professor Talbott, who is 57 and one of the leading physicians in the United States, contributed the article on 'Advances in Medicine' to our Special Number on 'Advances in Treatment' in October 1957.

YELLOW FEVER VACCINATION

HITHERTO, yellow fever vaccination has only been available at Regional Blood Transfusion Centres and certain hospital laboratories with special storage facilities and knowledge of necessary laboratory technique. Now that the vaccine is prepared in dried form and can be stored in an ordinary domestic refrigerator, local health authorities have been asked by the Ministry of Health to offer yellow fever vaccination to those requiring it. Local authorities providing this service are empowered to charge the vaccinated individual a sum covering the cost of the vaccine and its administration.

AMERICAN PSYCHIATRY

LAST autumn Dr. Cecil C. Beresford, the physician superintendent of The Retreat, York, paid a visit to the United States. In his recently published annual report for 1958 he makes some interesting comparisons between psychiatric practice in our two countries. Whilst 'the general standard of treatment given in our respective countries was about equal', 'in material things there is no doubt of their superiority; buildings, modern conveniences, and non-medical equipment, all being quite luxurious'. In social services, too, Dr. Beresford was 'most impressed', particularly in the American modification of the duties of social workers when working in a private as opposed to a state hospital. On the other hand, 'the British nurse still surpasses her American counterpart'. What he most envied, however, was 'the number of doctors, both of specialist and trainee rank, in every hospital. Being heavily subsidized each year from charitable funds, the private hospitals over there are able to employ perhaps two or three times the number of doctors found in any equivalent British hospital, and therefore organize a thorough and systematic training of their residents on a scale quite impossible in any but the few teaching psychiatric hospitals or university departments in this country'.

NARCOTIC DRUGS

DRUG addiction is not a serious problem in the United Kingdom, according to the Government's report on narcotic drugs for 1958. There are 442 known addicts (197 men and 245 women), 74 of whom belong to the 'medical and allied professions'. The most common drugs of addiction are morphine (174 addicts), pethidine (99 addicts), heroin (42 addicts), and methadone (35 addicts). In 1958, 148 persons were convicted of offences against the Dangerous Drugs Act and Regulations.

COMPULSORY EXAMS FOR DOCTORS

'A MANDATORY programme to force physicians to keep pace with medical progress' has been proposed by Dr. Gunnar Gundersen, president of the American Medical Association in 1958-59, according to *GP*. Among his recommendations was that holders of medical licences must demonstrate at intervals through re-examination that 'they have retained important basic knowledge and competencies and have kept up to significant advances'.

ANTIBIOTICS IN MILK

THE indiscriminate use of antibiotics in the treatment of cattle, particularly when injections are made directly into the udder, was deprecated by the WHO Expert Committee on Milk Hygiene, which met recently in Geneva. Many people, the Committee noted, are allergic to antibiotics and may therefore be affected by the consumption of milk from such cows. The Committee also drew attention to the fact that the new insecticides of the organo-phosphorus group should be used with great care in cowsheds and dairy installations so as to avoid the risk of the milk becoming contaminated.

POLIO VACCINE IN RUSSIA

FOUR million Soviet children have been vaccinated with the Sabin poliomyelitis vaccine. This is a vaccine prepared from live attenuated virus, and given orally—as opposed to the Salk vaccine in use in this country which is prepared from dead virus and is given parenterally. Enough of the Sabin vaccine has been produced in Russia to inoculate 12 million people. In Moscow the vaccine is said to have been successfully incorporated in syrup-filled bonbons.

HAWAII MEDICINE

HAWAII, which is shortly to become the 50th State of the United States of America, has 580 doctors and 32 hospitals for its 580,000 inhabitants. According to the *AMA News*, published by the American Medical Association, 'it offers many hurdles to the physician who would practise there'. Apart from anything else, the cost of living is 20% higher than in the United States, and there is no reciprocity with any of the constituent states. The A.M.A. comment is: 'Hawaii is beautiful, but it's not an island paradise for new physicians. Hawaii invites physicians to come as tourists, but advises them that opportunities to practise as residents are few'.

INTRA-UTERINE RINGS AND CONTRACEPTION

IN view of the wellnigh universal condemnation of the Graefenberg, or intra-uterine, ring as a means of contraception, it is of interest to note that the use of these rings is now being advocated in Japan. According to Atsumi Ishihama, of the department of obstetrics and gynæcology, Iwate Medical College, Morioka, they are not only reliable but free from serious undesirable effects provided they are used with care (*Yokohama med. Bull.*, 1959, **10**, 89). His conclusions are based upon two series of cases dealt with by himself, in 623 of which a metallic ring was used, and in 350 of which a polyethylene ring was used. In addition he has reviewed the results in 18,594 cases reported from 140 Japanese hospitals. Taking all these into consideration he claims an efficiency rate of 96.5%. There were said to be 'no serious side-effects'. The rings should not be used unless the genital tract is normal, and it is recommended that the wearer should be examined twice a year, and that the ring should be replaced with a new one annually.

CHLOROQUINE AND CARDIAC ARRHYTHMIAS

CHLOROQUINE sulphate is 'an effective and promising drug in the treatment of cardiac arrhythmias', according to Ch'en Hsi-Mou and Chou Ch'i-Lin (*Chin. med. J.*, 1959, **78**, 569). This conclusion is based upon their findings in a series of 13 cases: one of atrial extrasystoles, eight of ventricular extrasystoles, and four of atrial fibrillation. The initial dosage was 0.6 to 1 g. daily in divided doses by mouth, increased by 0.2 g. every third day until normal rhythm was restored or gastro-intestinal side-effects precluded further increase in dosage. Disappearance of the ectopic rhythm occurred in six cases, including two of those with atrial fibrillation, and 'marked improvement' in five. Treatment had to be discontinued in two cases, including one of atrial fibrillation, on account of the severity of the side-effects.

CHLOROSIS

IT is too early to bury chlorosis as a disease of merely historical interest, according to G. Marchal and his colleagues (*Progr. méd.* (*Paris*), 1959, **87**, 247). In support of this statement they report six cases which were seen in the hæmatology clinic of the Hôpital Brousais in the course of one year. They were all young women, aged 19 to 28. There was one mild case, two of moderate severity, and three severe cases. Large doses of iron by mouth remain the basis of treatment, but in severe cases this requires supplementation with blood transfusions and even folic acid. In discussing causation, it is considered that the almost invariable incidence of the disease in young women suggests an endocrine cause.

PUBLICATIONS

Clinical Effects of Electrolyte Disturbances is the proceedings of a conference held in London at the Royal College of Physicians earlier this year. It is an admirable review of a subject of growing importance to the clinician, and can be commended to those practitioners who wish to have an authoritative, yet reasonably simple and practical, review of the subject. (Pitman Medical Publishing Co. Ltd., price 20s.)

Current Drug Handbook 1959-60, by Mary W. Falconer, R.N., M.A., and H. Robert Patterson, M.S., PHARM.D., gives the essential details of a thousand currently used drugs in useful tabular form. Its value to the British reader is diminished by the absence of *B.P.* or approved names. Nevertheless the practitioner will find it a useful quick-reference book. (W. B. Saunders Co., price 19s.)

The Living Body, by C. H. Best, C.B.E., M.D., F.R.S., and N. B. Taylor, M.D., F.R.C.P.(C), has been completely reset in this fourth edition. As what the authors describe as 'a text in human physiology' it is one of the best books available

for the use of those members of senior forms who are studying biology at school. It would be equally valuable for students at teachers' training colleges. (Chapman & Hall, price 45*s*.)

Peripheral Nerve Injuries, by Ruth E. M. Bowden, D.SC., M.B., B.S.—As Professor Seddon indicates in his foreword, advances in the treatment of peripheral nerve injuries have depended largely upon the experience acquired in successive wars. In peacetime the occurrence of such injuries is too sporadic to encourage the development of either expertise in assessment or a high degree of special skill in management. This small handbook is a simple and readable presentation of the subject, illustrated by admirably clear line drawings, which should prove valuable to many who are occasionally called on to deal with these difficult cases. (H. K. Lewis & Co. Ltd., price 8*s*. 6*d*.)

Dorland's Pocket Medical Dictionary is the new title of the twentieth edition of the popular 'American Pocket Medical Dictionary'. Many new terms have been added and others redefined, and this handy little book continues to maintain the high standard of previous editions. (W. B. Saunders Co. Ltd., price 31*s*. 6*d*.)

Topics in Psychiatry, edited by T. Ferguson Rodger, M.B., F.R.C.P.ED., R. M. Mowbray, M.A., and J. R. Roy, M.B., M.R.C.P.ED., F.R.F.P.S.G., D.P.M.—This is the proceedings of a specialist conference in psychiatry held in Glasgow last year, largely for mental hospital officers and ancillary workers in the West of Scotland. Aspects of recent research in schizophrenia, psychosomatics, tranquillizers, mental deficiency and genetics are summarized with their practical applications. The authors and editors are to be congratulated on presenting recent knowledge so attractively. Contributions from biologists, geneticists and general physicians give this whole volume the 'feel' that psychiatry impinges closely upon general medicine and the hope that a fruitful marriage between the two will be possible (Cassell & Co. Ltd., price 20*s*.)

Orthopædics in General Practice: Is it Rheumatism Doctor?, by W. H. Gervis, M.B., CH.B., F.R.C.S., is an extraordinary little book designed to help the general practitioner in his treatment and disposal of patients with common orthopædic complaints. The author is apt to write in a kind of 'telegraphese' that is a little disconcerting and gives the impression of restlessness and 'Brownian movement'. The section devoted to 'The Foot' will be the most satisfying to the general practitioner, and it is difficult to think of another source where such useful information can be found so easily. The book is full of common sense, and that alone makes it worth while reading, and the questions that the author asks himself make the book attractive as well as informative. (William Heinemann (Medical Books) Ltd., price 10*s*. 6*d*.)

Ceylon Hospitals Formulary 1959 is an admirable little production, of which the compiling committee has every reason to be proud. Its general pattern follows that of the *British National Formulary*. (Department of Health, Colombo, Ceylon.)

Directory of Hospital Contributory Schemes Benefits and *Directory of Convalescent Homes in the Provinces* are the 1959 editions of the publications issued by the British Hospital Contributory Schemes Association at Royal Liver Buildings, 42 Baldwin Street, Bristol 1, price 10*s*. and 5*s*. respectively, post free.

OFFICIAL PUBLICATIONS

Domestic Food Consumption and Expenditure 1957 is the annual report of the National Food Survey Committee. One of the many interesting points brought out is 'the continued stability of British spending habits as between broad groups of commodities'. In the period covered by this report 18% of total domestic expenditure on food was devoted to milk, cheese and eggs, 32% to meat and fish, 16% to fruit and vegetables, 26% to cereals, fats, sugar and preserves, and 8% to all other foods. The comparable percentages in 1937 were 18, 30, 14, 27 and 11. (H.M. Stationery Office, price 8*s*. 6*d*.)

Strontium-90 in Human Diet in the United Kingdom 1958.—This report by the Agricultural Research Council presents a reassuring picture of the effect of 'fall-out' on our diet. It is based upon a country-wide survey. Milk was collected from over 200 depots, which between them handle more than 40% of the total milk produced in the United Kingdom. The mean concentration of strontium-90 in milk was estimated as 7 micro microcuries per gramme of calcium. In addition, representative samples of flour, potatoes and green vegetables were analysed. The major conclusion reached is that 'the ratio of strontium-90 to calcium in the United Kingdom diet during 1958 nowhere reached the level which, in the view of the Medical Research Council, would need to be greatly exceeded if the situation were to require immediate consideration; the average level was less than one-sixth of this limit', (H.M. Stationery Office price 4*s*.)

NOTES FROM THE CONTINENT

A European Newsletter

BELGIUM

Treatment of the obese diabetic.—The obese diabetic is a distinct clinical entity, quite different from the thin diabetic, according to Jean Pirart. Of the 30,000 diabetics in Belgium, 75% come into this category of obese diabetics. In spite of its apparently benign course—for example, the absence of ketosis—the danger of vascular and infectious complications must never be overlooked. Unlike the thin diabetic, the condition is partially reversible provided active treatment is instituted immediately the diagnosis is made, and is maintained. This consists of a low-calorie diet, with marked restriction of carbohydrate and fat intake, with the aim of obtaining as rapid as possible a fall in weight. Not only does such a diet control the diabetes, as shown by a lowering of the blood sugar and a disappearance of glycosuria, it also leads to an improved sugar tolerance and even—on occasions—to disappearance of all signs of diabetes. In addition, it saves the patient from all the expense and trouble of having to use insulin, prevents the onset of the vascular complications of diabetes and retains his weight at a reasonable level. In the author's experience this is the simplest and most effective form of therapy of the obese diabetic, and usually dispenses with the necessity for using either insulin or the oral hypoglycæmic compounds.

Intracranial aneurysms.—In a detailed report on the clinical and radiological findings in 54 consecutive cases of intracranial aneurysm, Professor G. Melot and his colleagues stress the importance of cerebral angiography in their diagnosis and localization. Such aneurysms, they point out, are far from rare, and are responsible for the majority of subarachnoid hæmorrhages. They can also be responsible for other clinical manifestations, depending upon their site and their size.

Electrophoresis of bronchial secretions.—As a result of their findings in 100 subjects, F. De Clercq and his colleagues consider that the protein content of bronchial secretions, as determined by electrophoresis, is of diagnostic value. In chronic infections of the lungs it provides information as to how much of the pulmonary reaction is inflammatory and how much is necrotic. It is also of value in carcinoma of the lung, particularly in deciding to what extent an inflammatory or suppurative element is present.

Photo-electric plethysmography.—Photo-electric plethysmography, according to J. L. Meirsman, is a valuable aid in the diagnosis of peripheral vascular disease. It has the added advantages of being relatively simple to use and of causing the patient a minimum of inconvenience. A single record in a given patient is of no value, nor are the records of different patients strictly comparable. What is of value is a comparison of records in a given patient obtained at different sites, and at different times, and before and after vasodilatation has been induced. It is said to have proved of value in deciding upon the appropriate treatment and in assessing the prognosis.

Chemotherapy in pulmonary tuberculosis.—In a review of the present status of chemotherapy in the treatment of pulmonary tuberculosis, R. Courtois and his colleagues express the view that if, after six months' intensive chemotherapy, the result is not satisfactory, then surgery should be resorted to without further delay. If, for any reason, surgery is not feasible, then chemotherapy (streptomycin + PAS + isoniazid) should be continued. It is very rare for all the mycobacteria to become resistant to all three drugs, and by continuing treatment there is a considerable decrease in the numbers of residual organisms. If the response to chemotherapy is satisfactory at the end of six months, treatment should be continued in order to reduce the risk of relapse. In the authors' experience relapse is rare after eighteen months of uninterrupted chemotherapy. The danger of increasing bacillary resistance by prolonged therapy must not be overstressed. Even though resistance develops, it is said that there is considerable evidence that resistant mycobacteria are less virulent than sensitive ones, and that this is particularly true of isoniazid-resistant organisms. The opinion is expressed that the value of chemoprophylaxis is still debatable.

Rheumatic pneumonopathy.—In reporting seven cases of rheumatic pneumonopathy, three of which proved fatal, J. Brichant and his colleagues contend that this should not be regarded as an epiphenomenon of acute rheumatism, but a manifestation of the disease in the same category as the articular and cardiac manifestations. The presenting symptom is dyspnœa, and, in the authors' experience, consolidation is not as rare as some contend. One of their cases closely simulated lobar pneumonia. The radiological picture is one of a fleecy infiltration of

the central zone of the lung, surrounded by a clear peripheral zone. In some cases the infiltration is more marked at the base of the lungs. The prognosis is poor, but not invariably fatal. Steroid therapy is sometimes of value if it is instituted in the early stages of the disease.

FRANCE

A new method of aortography.—A new method of aortography which is said to be safer than any of those at present in use has been described by F. Pinet and his colleagues. This consists of the injection of the contrast medium into a peripheral artery—usually the radial artery. A satisfactory 'counter-current' of the contrast medium is obtained by inducing a temporary phase of hypotension by means of trimetaphan. The hypotension lasts for only about five minutes and, because of the hypotension, only a relatively small amount of the contrast medium is required: 20 to 30 ml. It is recommended that the procedure be carried out under general anæsthesia. By this method, it is claimed, excellent pictures are obtained of the aorta and all its branches.

Laceration of the broad ligament.—J. Varangot and his colleagues have reported their findings in 30 cases of laceration of the broad ligament. This is usually the sequel of some obstetric complication such as dystocia or an abnormally rapid delivery, or may follow upon curettage carried out in the management of an abortion. The symptoms include abdomino-pelvic pain, dyspareunia, and dysmenorrhœa, and on examination there is found to be retroversion of the uterus with an abnormally mobile cervix. It usually involves the posterior layer of the ligament and is often accompanied by a varicocele of the uterine vessels, with serous fluid in the pouch of Douglas. Treatment consists of suture of the laceration and ligamentopexy.

The heart in typhoid.—The frequency of cardiac complications in typhoid fever has not been influenced by modern methods of treating the disease, according to J. Thiodet and his colleagues. As a result of an electrocardiographic and biochemical study of a hundred cases they conclude that the cardiac involvement is what they describe as a 'metabolic myocardosis', characterized by marked electrolyte disturbance —especially of potassium. They attribute this cellular disturbance of the myocardium to increased protein catabolism, low calorie intake, dehydration and pyrexia. Prevention consists of an adequate fluid and potassium intake. Should cardiovascular collapse occur, treatment consists of hypertonic glucose saline, potassium, insulin and full doses of strychnine. As the patient recovers, small doses of sympathomimetic drugs may be of value.

Infectious arthritis following intra-articular injections of hydrocortisone.—The increasing popularity of intra-articular injections of cortisone for the treatment of painful conditions of the joints is not without its dangers, and J. and R. Judet have drawn attention to the increasing frequency of infectious arthritis following this procedure. A certain number of these cases are subacute and may never be recognized, but others run a much more acute and alarming course. Treatment consists of the immediate administration of full doses of penicillin. Should pus collect this must be removed by arthrotomy and the joint then be immobilized for several days—either in plaster of Paris or by means of extension. As soon as all signs of inflammation have disappeared, the joint is gradually mobilized. In order to prevent this serious complication, stress is laid upon the necessity of always treating an intra-articular injection as a surgical procedure demanding strict asepsis in its performance.

International Conference on Medical Electronics.—The second international conference on medical electronics, which was held in Paris earlier this summer, provided a vivid illustration of the impact of science on medicine. Not so very long ago we had only electrocardiography and electroencephalography. Now we have electro-oculography which can diagnose hemiopia and cerebellar syndromes by registering abnormal movements of the eyes, photo-electric cells which can measure blood flow in the lungs and pulmonary ventilation, and electronic stimulators (or pacemakers) of the heart. At the same time, electronics are revolutionizing laboratory procedures, and apparatus is now available which will record the antibiotic sensitivity of bacteria, or count and record the number of cancer cells in a specimen just as efficiently as the automatic recorders now count the number of red cells in a specimen of blood.

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THE PRACTITIONER
Fifty Years Ago

'Indeed, what is there that does not appear marvellous when it comes to our knowledge for the first time?'—Pliny the Elder, *Historia Naturalis*, Bk vii, sec. 6.

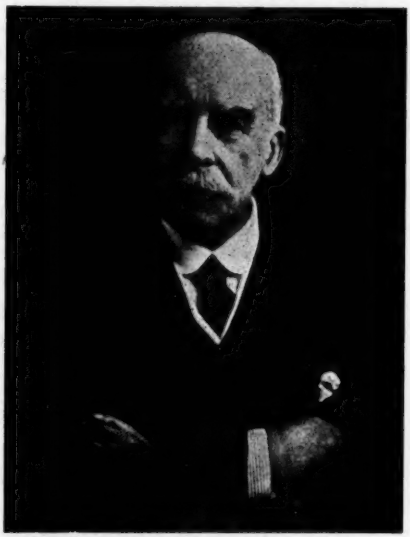
SEPTEMBER, 1909

'NOTES by the Way' begin by congratulating all concerned upon the success of the 77th Annual Meeting of the British Medical Association held at Belfast under the presidency of Sir William Whitla, Professor of Materia Medica and Therapeutics at Queen's College: 'Many members of the Association attended the gathering, and the presence of the Lord Lieutenant of Ireland and the Countess of Aberdeen throughout the proceedings rendered the occasion memorable in the annals of the Association. A large number of distinguished foreign medical men were entertained by the citizens of Belfast, whose hospitable labours were most fully appreciated'.

Under the heading 'Coley's Fluid' the Editor writes: 'The occasion of the visit of Dr. W. B. Coley was taken full advantage of by the medical profession in this country, and Dr. Coley will not easily forget the enthusiastic reception accorded to him by the distinguished audience that crowded the large hall of the Royal Society of Medicine to hear him deliver an address on the treatment of sarcoma by Coley's fluid. A large number of those present had had unsuccessful results in cases treated with the preparation of bacterial toxins known as Coley's fluid, and the closest attention was paid to that part of the address in which Dr. Coley explained how much success depended upon a judicious determination of the dosage for a given case. . . . The reason why so many medical men regard the use of Coley's fluid as useless was explained thus: Occasionally the physician has heard of the mixed toxins in cases of sarcoma, and if he has read of the method he has probably forgotten the details, and has little faith in its value. Now and then a surgeon is found who takes the time to give the matter special thought, and who is willing to give the patient the benefit of a trial with the toxins. He begins with some fears and more doubts, and when he sees the patient in one of the severe chills . . . he hesitates to go on or is unable to instil into the patient the courage and confidence so necessary to enable him to continue the treatment to a successful termination'.

In his last paper on the subject (*Glasgow Medical Journal*, 1936, **126**, 49-86; 128-164), William Bradley Coley (1862-1936) recalled the sympathetic encouragement he had received from Lister in the early years when any new method of treating inoperable malignant tumours was looked upon with doubt and scepticism.

The opening article, 'Cancer of the Breast, and its Early Diagnosis', is contributed by Anthony A. Bowlby, C.M.G., F.R.C.S., Surgeon to St. Bartholomew's Hospital: 'I wish it could be written as large as possible in the mind



Sir Anthony A. Bowlby, Bt., K.C.B., K.C.M.G., K.C.V.O., D.C.L., F.R.C.S.

of the public that—*Cancer is painless in its early stage*. It seems impossible at present to make people thoroughly understand this. Over and over again one is told by a patient: "Yes, I have known of a lump there during the last six months, but as it did not cause me any pain I did not suppose it could do me any harm".'

Sir Anthony Alfred Bowlby, Bt. (1855-1929), was elected assistant-surgeon at St. Bartholomew's Hospital in 1891, full surgeon in 1903, and consulting surgeon in 1919. He served as president of the Royal College of Surgeons of England from 1920 to 1923. During the South African War he was senior surgeon in charge

of the Portland Hospital, and during the first world war he was consulting surgeon to the British Expeditionary Force and to the Second Army, and afterwards Adviser in Surgery to the British Forces in France with the rank of major-general. In 1910 he became surgeon-in-ordinary to George V. He was knighted in 1911 and created K.C.M.G. in 1915, K.C.V.O. in 1916, K.C.B. in 1919, and a baronet in 1923. As a clinical teacher Bowlby was lucid, dogmatic, and practical. Known as the 'Baron' or the 'Baron of Bapaume', he made friends easily and possessed sound common sense and cool judgment. He spoke forcibly and fluently with a characteristic jerking of the whole body, but wrote with difficulty.

H. Batty Shaw, M.D., F.R.C.P., Physician to University College Hospital, presents a 'Review of Diseases of the Blood'; J. E. R. McDonagh, F.R.C.S., R. Müller, and G. Morawetz discuss 'The Serum Diagnosis of Syphilis'; J. Courtenay MacWatters, M.R.C.S., L.R.C.P., Hon. Medical Officer, Almondsbury Memorial Hospital, describes 'Vaccine Therapy in General Practice'; William Sheen, M.S., F.R.C.S., Surgeon to the Cardiff Infirmary, discourses on 'The Etiology of Hernia'; and R. C. Elsworth, M.D., M.C., F.R.C.S., Surgeon to Swansea Hospital, deals with 'Chronic Indigestion Considered as a Surgical Disease'.

An unsigned contribution 'Mountaineering and Health', recalls the story of the English writer and critic, John Addington Symonds, who was suffering from consumption and announced his intention of 'pitching his camp in the high Alps': 'Sir William Jenner warned him that, if he did so, he would infallibly leave his "vile body" in the hands of the Swiss doctors; and it might be hard to find a case in which so great a physician has made himself responsible for so inaccurate a prognosis'.

'Notes from Foreign Journals' describe 'a treatment which at once relieves the pain of bites from mosquitoes and gnats, and the stings of wasps and bees . . . iodine in saponated petroleum (30 to 40 grains to the ounce). A few drops of this rubbed over a mosquito-bite acts as by magic'.

Among the books reviewed this month are W. Hale White's 'Common Affections of the Liver' ('a welcome addition to medical literature'); Macleod Yearsley's 'A Text-book of Diseases of the Ear'; William Osler's 'An Alabama Student, and other Biographical Essays' ('it is scarcely possible to conceive of a more helpful and pleasant pastime, for a physically jaded and mentally wearied medical practitioner, than an occasional half-hour devoted to Professor Osler's admirable volume'); and the fourth edition of 'An Index of Treatment', edited by Robert Hutchison and H. Stansfield Collier.

W. R. B.

ST. ANDREWS HOSPITAL, NORTHAMPTON

FOR NERVOUS AND MENTAL DISORDERS

President—THE EARL SPENCER

Medical Superintendent—THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

This Registered Hospital is situated in 130 acres of park and pleasure grounds. Voluntary patients, who are suffering from incipient mental disorders, or who wish to prevent recurrent attacks of mental trouble; temporary patients, and certified patients of both sexes are received for treatment. Careful clinical, biochemical, bacteriological and pathological examinations. Private rooms with special nurses, male or female, in the Hospital or in one of the numerous villas in the grounds of the various branches can be provided.

WANTAGE HOUSE

This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of Mental and Nervous Disorders by the most modern methods; insulin treatment is available for suitable cases. There is an Operating Theatre, a Dental Surgery, an X-Ray Room, an Ultra-Violet Apparatus, and a Department for Diathermy and High-Frequency treatment. It also contains Laboratories for biochemical, bacteriological, and pathological research. Psychotherapeutic treatment is employed when indicated.

MOULTON PARK

Two miles from the Main Hospital there are several branch establishments and villas situated in a park and farm of 650 acres. Milk, meat, fruit, and vegetables are supplied to the Hospital from the farm, gardens, and orchards of Moulton Park. Occupational therapy is a feature of this branch, and patients are given every facility for occupying themselves in farming, gardening, and fruit-growing.

BRYN-Y-NEUADD HALL

The seaside house of St. Andrews Hospital is beautifully situated in a Park of 330 acres, at Llanfairfechan amidst the finest scenery in North Wales. On the north-west side of the Estate a mile of sea coast forms the boundary. Patients may visit this branch for a short seaside change, or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout fishing in the park.

At all the branches of the Hospital there are cricket grounds, football and hockey grounds, lawn tennis courts (grass and hard courts), croquet grounds, golf courses, and bowling greens. Ladies and gentlemen have their own gardens, and facilities are provided for handicrafts, such as carpentry, &c.

For terms and further particulars apply to the Medical Superintendent (Telephone: No. 4354, three lines, Northampton), who can be seen in London by appointment.